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VASCULAR SUPPLY OF THE SPINAL GANGLIA

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A great deal of interest has been taken in the structure and pathology of the spinal ganglia (Dogiel,[1] Ranson,[2] de Castro,[3] Truex[4] and bibliographies by de Castro[3] and Truex[4]), but hardly any attention has been given to their circulatory system.

The blood supply and the drainage of the spinal cord have been studied by Adamkiewicz,[5] Kadyi,[6] Ziehen,[7] Suh and Alexander[8] and Herren and Alexander.[9] However, little is known about the vascular supply of the spinal ganglia, which lie well hidden in the intervertebral foramens. At routine autopsy these organs are never exposed from the

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1. Dogiel, A. S.: Der Bau der Spinalganglien des Menschen und der Säugetiere, Jena, Gustav Fischer, 1908.

2. Ranson, S. W.: The Structure of the Spinal Ganglia and of the Spinal Nerves, J. Comp. Neurol. **22**:159-169, 1912.

3. de Castro, F.: Sensory Ganglia of the Cranial and Spinal Nerves, Normal and Pathological, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, pp. 91-143.

4. Truex, R. C.: Morphological Alterations in the Gasserian Ganglion Cells and Their Association with Senescence in Man, Am. J. Path. **16**:255-268, 1940.

5. Adamkiewicz, A.: Die Blutgefässe des menschlichen Rückenmarkes, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **85**:101-130, 1882.

6. Kadyi, H.: Ueber die Blutgefässe des menschlichen Rückenmarks; Nach einer im XV. Bande der Denkschriften der math.-naturw. Classe der Akademie der Wissenschaften in Krakau erschienenen Monographie. Aus dem polnischen Übersetzt vom Verfasser, Lwów, Poland, Gubrynowicz & Schmidt, 1889.

7. Ziehen, T.: Zentralnervensystem, in von Bardeleben, K.: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, 1903, vol. 1, pt. 1, pp. 68-76.

8. Suh, T. H., and Alexander, L.: The Vascular System of the Human Spinal Cord, Arch. Neurol. & Psychiat. **41**:659-677 (April) 1939.

9. Herren, R. Y., and Alexander, L.: Sulcal and Intrinsic Blood Vessels of Human Spinal Cord, Arch. Neurol. & Psychiat. **41**:678-687 (April) 1939.

ventral side, and after exposure of the spinal cord from the dorsal aspect the ganglia are usually removed incompletely, if at all, together with the roots or alone, with no connecting structures. Thus their relations with the segmental vessels are usually destroyed.

MATERIAL AND METHODS

1. Autopsy material from 16 adult patients, their ages ranging from 28 to 84 years, who had not suffered from diseases or disturbances of the nervous system, from 21 children[10] aged 3 days to 10 years and from 4 newborn infants was studied. In 8 of the cases three or four segments of the vertebral column, including the spinal cord, the vertebral canal and the intervertebral tissues, were dissected out *in toto*. The spinous processes with the adjacent parts of the vertebral

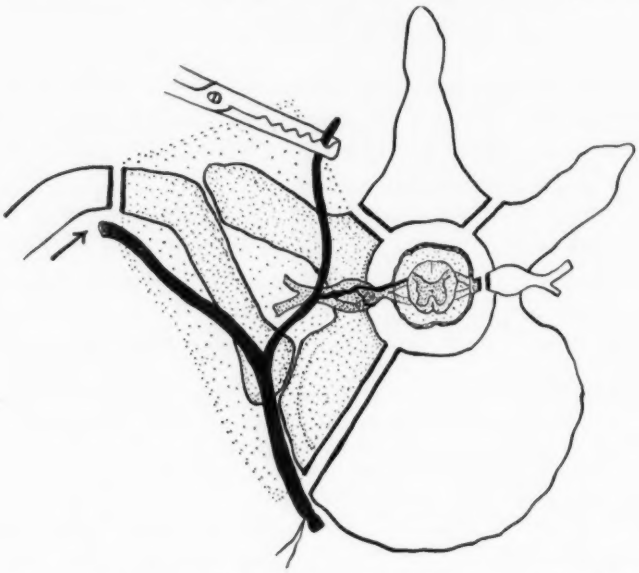

Fig. 1.—Diagram of a thoracic segment in man, illustrating the mode of excision and site of injection (arrow). The injected area is shown as stippled. The proximal part of the intercostal artery has been ligated.

arches were removed and discarded. Then the lateral thirds of the vertebral bodies together with the transverse processes and the surrounding tissue, containing the segmental vessels, were excised for examination. The cord and the dura were left intact with this block of tissue by merely sectioning the roots of the opposite side (fig. 1). Injection with a mixture of 1 part india ink and 3 parts of a 10 per cent concentration of neutral solution of formaldehyde U. S. P. has proved to be successful in investigations of vessels of the nervous system (Alexander and Suh[11]). Injections were made into two alternating segmental

10. Dr. Sidney Farber contributed spinal ganglia from his autopsy material at the Children's Hospital, Boston.

11. Alexander, L., and Suh, T. H.: Arterial Supply of Lateral Parolivary Area of the Medulla Oblongata in Man, Arch. Neurol. & Psychiat. **38**:1243-1260 (Dec.) 1937.

arteries, leaving one segment between them without injection, or into the vertebral artery. Major leaks were tied off or clamped. Examination was made first by gross preparation of the vessels and exposure of the spinal ganglion by means of a bone cutter; later the ganglion was cut into frozen sections, 250 microns thick. By this method, devised by Wislocki [12] for thick pyroxylin sections, vessels can be traced for a considerable distance after the sections are dehydrated, cleared and mounted unstained.

One specimen was injected with colored revertex rubber mass for gross dissection.

Additional spinal ganglia from other, uninjected segments and from identical segments from 31 other subjects were removed for staining by the benzidine, hematoxylin-eosin, Masson trichrome and Bodian protein silver (protargol) methods. Sections prepared by the last three stains were used for general histologic information.

The benzidine sections, prepared from frozen sections 250 microns thick and stained after the modification by Doherty, Suh and Alexander [13] of the Lepehne [14]-Pickworth [15] method, were used as controls in order to avoid mistakes in interpretation, which may arise from studying the vascular pattern of injected preparations. Only such peculiarities of the vascular pattern as were also present in benzidine-stained slides were considered; others were neglected as artefacts.

2. Injection of the entire body, which makes it possible to compare all the ganglia of an individual subject, could not be made in human material. This procedure was carried out in the Macacus rhesus monkey. The vascular system, while the body was still warm, was flushed out with a solution of sodium chloride injected into the ascending aorta and drained from the right auricle. Then 1,500 cc. of a mixture of india ink and solution of formaldehyde was injected slowly. The dural sac was exposed anteriorly by resecting the median parts of the vertebral bodies and disks, and posteriorly by removing the spinous processes and the arches. After dissecting the structures in the intervertebral foramens, or in the homologous spaces in the sacrum, under the binocular dissection microscope, several ganglia were cut into frozen sections, 250 microns thick. Others were removed, together with their roots, dura and vessels, dehydrated and cleared *en masse* in a benzyl benzoate–methyl salicylate mixture. The dissection microscope permitted a three dimensional comprehension of the periganglionic and intraganglionic vessels.

GENERAL ANATOMIC CONSIDERATIONS

Before the results thus obtained are reported it may be advisable to review briefly some well established anatomic facts. For more detailed information the reader is referred to the respective chapters on

12. Wislocki, G. B.: The Vascular Supply of the Hypophysis Cerebri of the Cat, Anat. Rec. **69**:361-387, 1937.

13. Doherty, M. M.; Suh, T. H., and Alexander, L.: New Modifications of the Benzidine Stain for the Study of the Vascular Pattern of the Central Nervous System, Arch. Neurol. & Psychiat. **40**:158-162 (July) 1938.

14. Lepehne, C.: Zerfall der roten Blutkörperchen beim Icterus infectiosus (Weil), Beitr. z. path. Anat. u. z. allg. Path. **65**:163-226, 1919.

15. Pickworth, F. A.: A New Method of Study of the Brain Capillaries and Its Application to the Regional Localization of Mental Disorder, J. Anat. **69**: 62-71, 1934.

angiology by Ziehen,[7] Tandler [16] and Gray [17] and to other sources in the literature.

The dorsal division of a segmental artery gives off branches to the corresponding vertebra (Forssman and Petrén [18]) and one spinal branch, which enters the intervertebral foramen and is often united with the artery supplying the vertebra. The ramus spinalis divides into an anterior and a posterior radicular artery. These supply the roots by fine arteriae radicinae, pierce the dura near the roots and finally join the anterior and the posterior arterial trunk of the cord, respectively. A certain number of these branches are significant tributaries to the circulation of the spinal cord, while the others, in adult man as well as in the newborn child, are vestigial or rudimentary (Suh and Alexander [8]). After having given off the spinal branch the remainder of the dorsal division of the segmental artery follows the dorsal division of the spinal nerve and supplies the paramedian region of the back. This holds true for the arteriae intercostales, lumbales, iliolumbales, or lumbales imae, and sacrales laterales. The cervical region differs insofar as the spinal branches of the arteria cervicalis ascendens enter the intervertebral foramens after union with the spinal branches from the arteria vertebralis and arteria cervicalis profunda. Thus, the arteria vertebralis (for the first to the sixth cervical vertebrae) and the arteria cervicalis profunda (for the lower cervical segments) are supplemented by the spinal branches of the arteria cervicalis ascendens. However, near the spinal ganglion there is to be seen the same arrangement of arteries as in the lower (e. g., thoracic) segments, for the branches of the arteria cervicalis ascendens anastomose with the vertebral and the deep cervical arteries before they give off their spinal branches.

With respect to the veins of the region in question, various authors have described rich internal vertebral plexuses (epidural), which communicate by means of intervertebral veins, situated in the intervertebral foramens, with the external anterior and the posterior vertebral plexus and with the dorsal divisions of the segmental veins. Valves at the point of emptying into the segmental veins prevent reflux into the vertebrospinal system. Fine venous plexuses surround the nerves passing through the intervertebral foramens, their relations to the spinal nerves thus resembling those of the cranial nerves within their bony canals. The radicular veins of the cord drain into the epidural plexuses.

RESULTS OF INTRAVASCULAR INJECTIONS

Injection of an intercostal artery usually fills first one of the arterial branches on the surface of the spinal cord or on the intradural surface of its roots. This proves to be the most direct path of the arterial current. There was not always a "significant" radicular artery (Suh and Alexander [8]) in the same segment, but a radicular artery was never lacking in these cases. Leakage from the adjacent segmental arteries was never observed. In some cases considerable leakage from the distal

16. Tandler, J.: Lehrbuch der systematischen Anatomie, Leipzig, F. C. W. Vogel, 1926, vol. 3.

17. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936.

18. Forssman, G., and Petrén, T.: Die arterielle Versorgung der Brustwirbelkörper, Anat. Anz. **88**:167-178, 1939.

opening of the segmental vein was encountered, although subsequent microscopic examination showed poor injection of the spinal ganglion. (All spurting vessels were clamped off or ligated, if possible, after a short period of leaking.) The most complete injections of the spinal ganglion were obtained by continuing the injection until the adjacent intercostal veins began to leak, which they were allowed to do for some time. The vessels of the spinal ganglion and of its capsule were never filled by injecting one or both adjacent segments. However, filling of some epidural veins could be obtained. The veins of the spinal ganglion, therefore, anastomose freely with those of other segments. The arteries supply the ganglia according to a strictly segmental plan, and the ganglia do not receive arterial blood from the cord or from the arterial systems of adjacent ganglia. The arteries which enter the ganglion seem to represent a side path or side shunting of the segmental arterial stream and can stay poorly filled even while the intercostal spinal circulation is well injected.

Injection into the vertebral artery from a point 1 inch (2.5 cm.) below the scalenovertebral angle did not reach the seventh and eighth cervical spinal ganglia, but the fifth and sixth cervical ganglia were completely injected. This suggests that there is a rather sharp demarcation between the province of the arteria vertebralis and that of the arteria cervicalis profunda.

ARTERIES OF THE SPINAL GANGLIA

The posterior division of the segmental (e. g., intercostal) artery shows some variations. It crosses over (fig. 2*A*) or under (fig. 2*B*) the lateral (distal) part of the spinal ganglion or the common trunk of the spinal nerve and gives off small branches to both divisions of the nerve (fig. 2*A*). Then it follows the posterior division of the nerve. The spinal branches arise in front of or behind the ganglion as a common trunk (fig. 2). The vertebral artery often releases dorsal and spinal branches independently (fig. 3).

In segments in which the anterior spinal branch becomes a "significant" anterior radicular artery (Suh and Alexander [8]), the posterior radicular artery usually arises as its offshoot (fig. 2*A*). In segments showing a strong (significant) posterior radicular artery, the small (insignificant) anterior radicular artery usually arises as its offshoot and may travel over the ganglion (fig. 2*B*). In such segments (with a large [significant] posterior radicular artery) it was often observed that the entire dorsal division of the segmental artery took its course below the spinal nerve or the ganglion, before giving off its spinal branches (fig. 2*B*). Arteries to the vertebra arise frequently from the spinal branch and from the dorsal division; they were omitted in the drawings.

The posterior spinal branch divides into two or three small arteries, which often communicate with the anterior spinal branch and with each other. They either meet again by gradual approach or form an arcade on the surface of the fibrous capsule of the ganglion (fig. 2). One of the branches continues as the posterior radicular artery and pierces the

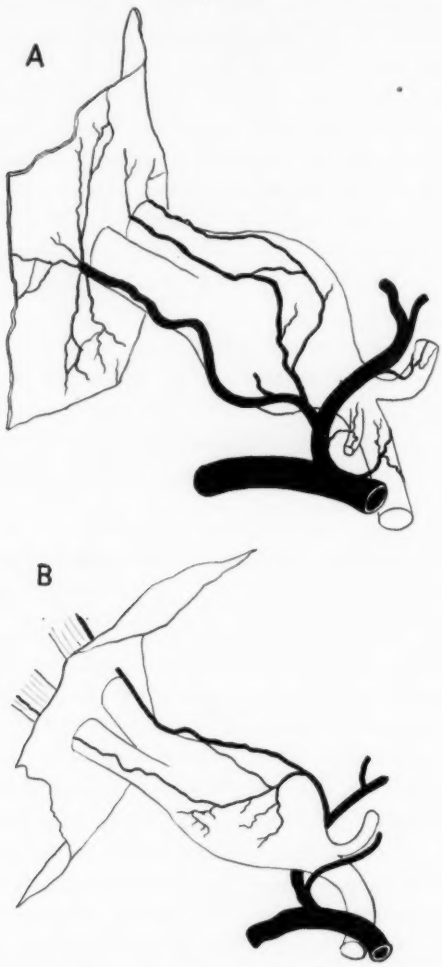

Fig. 2.—*A*, arteries of the seventh thoracic spinal ganglion of the rhesus monkey, with a significant anterior radicular artery. *B*, arteries of the third thoracic spinal ganglion of the rhesus monkey. The spinal branch of the segmental artery releases a significant posterior radicular artery. Note the dorsal division of the segmental artery, crossing below the spinal nerve.

dura. A small (insignificant) radicular artery runs closely adherent to the root; the large (significant) radicular arteries enter the dura,

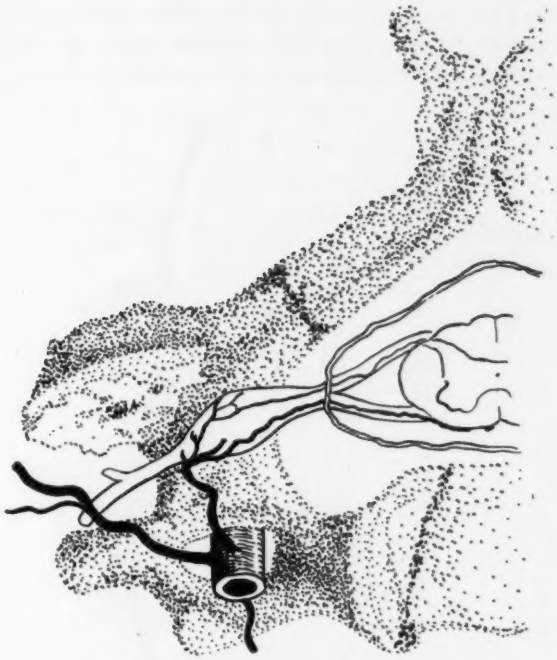

Fig. 3.—Diagram of the fifth cervical spinal ganglion of man, with the arteries exposed from above. Note the significant anterior radicular branch and the muscle branches arising from the vertebral artery. The vertebra is shown as stippled.

Fig. 4.—Diagram from the same specimen as that shown in figure 2 *A*, The dura mater has been split anteriorly to expose the inner surface of the dura and to show the proximal distribution of the arteries.

sometimes 1 mm. away from the radix. The radicular arteries give off fine branches to the spinal dura (fig. 2 *A*). These pass straight up and down to meet their fellows from the adjacent segments; others cross toward the midline, anastomosing with the meningeal branches from the opposite side.

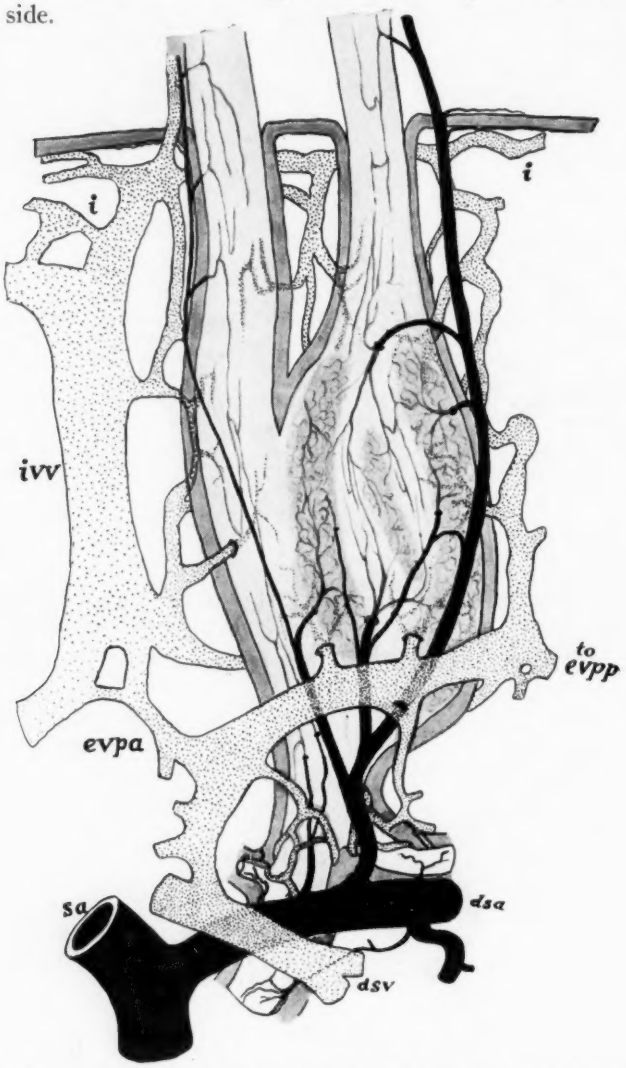

Fig. 5.—Diagram showing arteries (solid black) and veins (stippled) around and within the spinal ganglion. The dura, the fibrous sheath and the gray substance are indicated in gray tone. The intrinsic vessels fade off into the ganglion, as observed in translucent Spalteholz specimens. Here, *i* indicates internal vertebral plexus; *ivv*, intervertebral vein (in situ below the ganglion); *evpa*, external anterior vertebral plexus; *to evpp*, branch to external posterior vertebral plexus; *sa*, segmental artery; *dsa*, dorsal division of segmental artery, and *dsv*, dorsal division of segmental vein.

Having pierced the dura, the radicular vessels release again small branches for the inner dural surface and continue toward the cord, together with the nerve roots (fig. 4). After the radicular arteries enter the dural canal their caliber is always reduced. Insignificant radicular arteries run closely adherent to the root and are of very small caliber. They seem to be exhausted by furnishing the arteries for the spinal ganglion or the root. After their entrance into the dural space they are

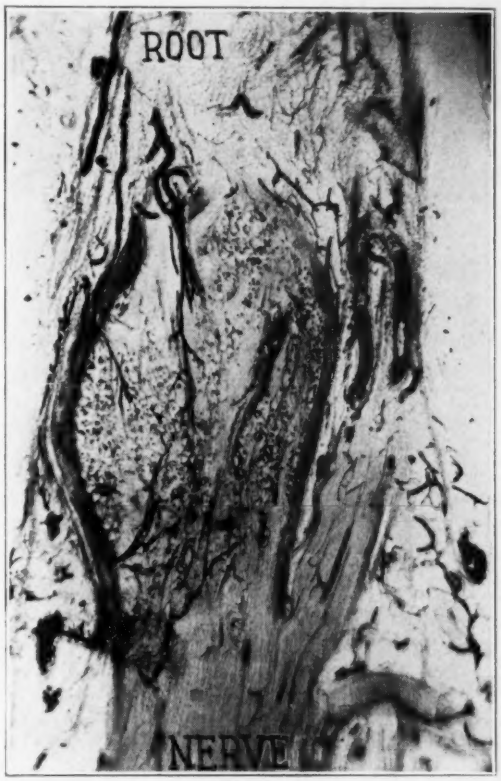

Fig. 6.—Photomicrograph (× 10) of the third thoracic spinal ganglion in man after injection. Note the recurving axial artery which enters the ganglion near its proximal (medial) pole. To the left of it an accompanying vein is seen. Two other arteries enter the periphery from the left margin—the one nearer the nerve entering in the main direction of the blood stream and the one nearer the root in a recurrent direction.

sometimes hardly distinguishable from the precapillaries running within the root.

The arteries on the surface of the spinal ganglion form a few slender meshes or arcades, as already indicated, and furnish two sets of vessels for the ganglion (fig. 5).

Figure 7

(See legend on opposite page)

The vessels of the first category pierce the dural fibrous sheath at right angles or obliquely at various points (figs. 5 and 6) and subdivide at rather wide angles into arterioles, which in turn supply the capillary networks of the extensive gray masses at the periphery of the ganglion. Some of the branches reach the central portion of the ganglion, where they meet the arteries of the second category. These enter near either extremity of the spinal ganglion (figs. 6 and 7), those at the medial pole frequently by way of arc-shaped channels (fig. 6), recurving from the stem of the main spinal vessel and then running in a more or less axial orientation straight through the white matter (figs. 5 and 6). They supply the capillaries of the gray masses in the central portion of the spinal ganglion and the long slender capillary loops of the white matter. In the lower cervical, upper thoracic and lumbar segments these longitudinal arteries run frequently through the entire ganglion. Small arterioles within the posterior roots anastomose with the capillary network at the medial pole of the ganglion (fig. 5) or with the longitudinal capillary and precapillary branches in its white matter. The arteries within the roots originate from the radicular arteries and pierce the dural sheath around the radix. The lateral pole of the ganglion, however, contains mostly terminal capillary loops, which anastomose poorly, or not at all, with the capillaries of the spinal nerve. The small arteries which enter the spinal nerve give rise to longitudinal capillary loops by T-shaped splitting, finally resulting in a longitudinal long-meshed pattern with short stepladder-like interconnections (fig. 7), thus confirming the findings of Petrovits and Szabó [19] in regard to the vessels of peripheral nerves.

The lamellae and strands of white substance within the spinal ganglia and both roots contain relatively few capillaries, the loops of their loose and wide-meshed capillary bed being long and generally parallel with the course of the fibers. In the gray matter of the spinal ganglion abundant and dense capillary networks are observed. Their meshes are released from fairly short precapillary arterioles and show a frequently and irregularly curved, or even tortuous, course. Almost every individual ganglion cell is surrounded by its own loop or loops.

19. Petrovits, L., and Szabó, Z.: Die arterielle Versorgung der Gliedmassennerven, Anat. Anz. **88**:392-404, 1939.

EXPLANATION OF FIGURE 7

Photomicrograph (× 20) of the fifth thoracic spinal ganglion in man after injection. Note the rich capillary network in the gray masses of the ganglion, contrasting with the long, slender, predominantly parallel capillary and precapillary channels in the roots and nerve.

VEINS OF THE SPINAL GANGLIA

The blood is collected by relatively large veins within the ganglion. They unite at obtuse angles, thus forming larger vessels, which are more numerous at the periphery and the poles. They pass through the fibrous sheath to join a superficial venous plexus (fig. 8). Those which drain the proximal anterior aspect of the ganglion pass into two or three vessels, situated between the roots. These minute venous interradicular plexuses receive in addition tributaries from the veins of the anterior root (figs. 5 and 6). Figure 7 shows a Y-shaped vein between the ganglion and the anterior root, which drains both structures. The small intrinsic venules of the roots pierce the radicular dural sheath and empty into the surrounding veins or into the interradicular veins. In those segments in which the anterior and posterior radicular sheaths are separated

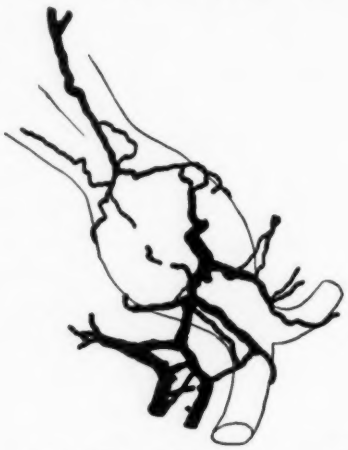

Fig. 8.—Diagram of the fifth lumbar spinal ganglion of man after injection. Only the veins are shown. Note the intervertebral vein at the lower left portion of the diagram, connected with the dorsal branch of the segmental vein, which travels over the ganglion. At the top a branch of the internal vertebral plexus is seen.

merely by a dural septum veins are plainly visible within this septum. The intradural space, however, does not contain plexiform veins. Just one radicular vein, significant in some segments, small or vestigial in others, is observed. It lies closely adherent to the root, usually on its cranial circumference.

All these veins join the rich extradural plexus which surrounds the fibrous sheath of the spinal ganglion, mainly on its posterior aspect. The anterior aspect of the plexus shows a somewhat poorer development (fig. 5). This plexus consists of tortuous veins, anastomosing with each other and receiving as tributaries the intrinsic veins of the ganglion, which pierce its sheath. The veins emerging from each pole

of the ganglion are collected in a vascular collar, which surrounds each pole more or less completely. The dorsal division of the segmental vein is frequently part of the collar-like formation of the lateral pole of the ganglion (figs. 5 and 8). The venous collar at the medial pole (fig. 7) is probably identical with the veins described by Elman [20] and Wislocki,[21] who found them in relation to arachnoidal cell clusters at the roots, serving for absorption of cerebrospinal fluid. Prior to Elman and Wislocki, Marburg [21a] had described veins which simulate cancerous spaces and which reach the posterior roots together with arachnoid tissue, the latter undergoing progressive hypertrophy with advancing age.

The venous plexus around the ganglion is continued into the fine plexuses at the dural radicular sheath and about the spinal nerve. The intervertebral vein, which connects the internal with the external vertebral plexus and which travels on the periosteum of the caudal wall of the intervertebral foramen, is also in communication with the periganglionic plexus. Hence the veins of the spinal ganglia drain into the internal and the external vertebral plexus, as well as into the dorsal division of the segmental vein.

CAPILLARY BED OF THE SPINAL GANGLION

While the capillaries in the white fascicles of the ganglion seem already to have been sufficiently described, the rich capillary plexuses around the neurons call for a more detailed discussion.

In the rhesus monkey one finds a regular network, made up of capillary channels of almost constant caliber; formation of beads does not occur, save for a few localized dilatations, which never exceed the double diameter of the parent capillary (figs. 9 and 10). This arrangement is similar to the capillary pattern shown in other parts of the central nervous system.

In man, however, the appearance of the capillary pattern in the spinal ganglia is fundamentally different from the pattern seen in the rhesus monkey or in any other part of the central nervous system of man or animals. This difference is most striking in adult man, from the third decade of life on, but a suggestion of it is already noticeable in newborn infants and children within the first decade of life.

The spinal ganglion of the newborn shows occasional beadlike dilatations of the capillaries and precapillaries, the diameter of which may be about three times the width of the parent vessel (figs. 11 and 12).

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20. Elman, R.: Spinal Arachnoid Granulations with Especial Reference to the Cerebro-Spinal Fluid, Bull. Johns Hopkins Hosp. **34**:99-104, 1923.

21. Wislocki, G. B.: Cytology of the Cerebrospinal Pathway, in Cowdry, E. V.: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1483.

21a. Marburg, O.: Zur Pathologie der Spinalganglien, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **8**:103-189, 1902.

In children more than 3 years of age, but still within the first decade of life, these beadlike irregularities of caliber are slightly larger, reaching sometimes five times the diameter of the vessel in the course of which

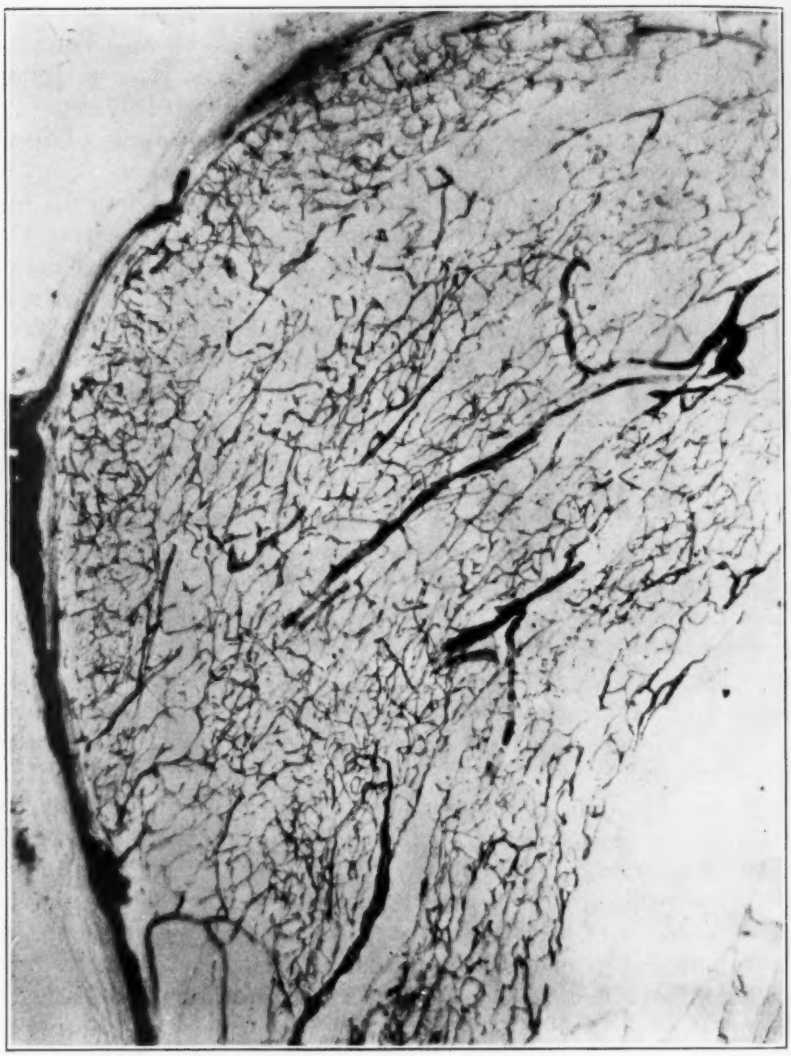

Fig. 9.—Photomicrograph (× 40) of a lumbar spinal ganglion of an adult rhesus monkey after injection. Note the regular and uniform capillary pattern.

they occur. The most striking beadlike and ampullar dilatations, however, are found in the capillary bed of spinal ganglia of adult human beings from the third decade of life (figs. 13 and 14). They consist of

beadlike or ampullar dilatations of capillary and precapillary channels which reach eight to twenty times the size of the diameter of the vessel in the course of which they occur. Those occurring in the course of capillaries may measure from 40 to 100 microns in diameter. They are equally striking in injected and in benzidine-stained preparations,

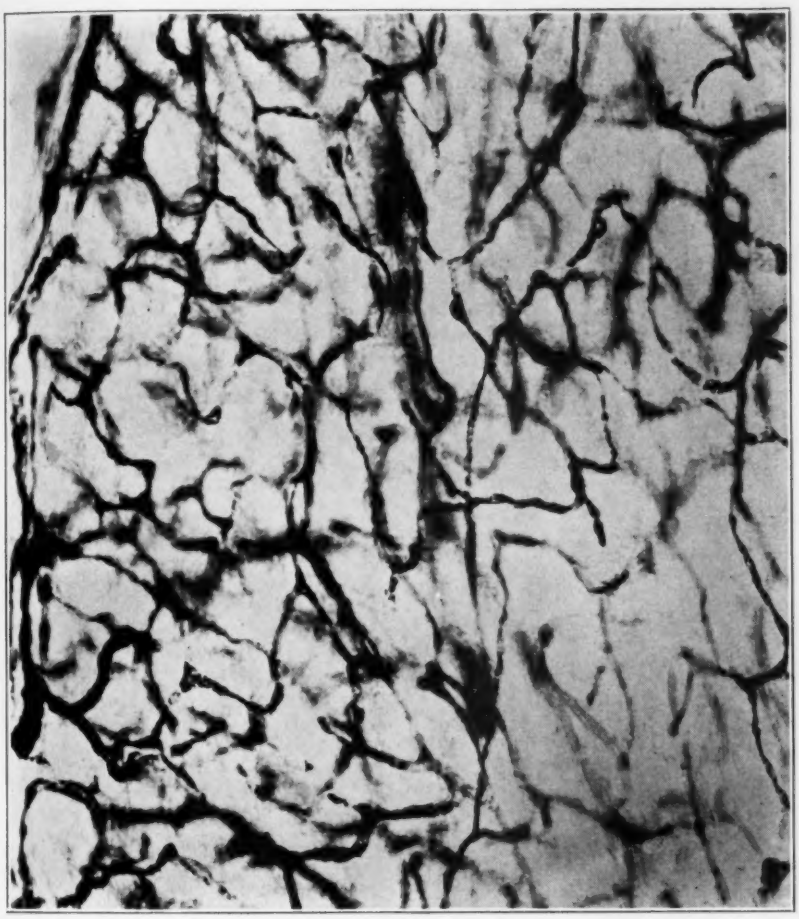

Fig. 10.—High power photomicrograph (× 175) from the specimen a section of which is shown in figure 9. Note the essentially regular and uniform caliber of the capillaries, except for occasional dilatations, not exceeding twice the diameter of the capillaries in the course of which they occur.

and we have satisfied ourselves that they are not due to artefacts of injection. After our attention was drawn to them by the injected and the benzidine-stained preparations, we were able to identify them in paraffin sections stained with hematoxylin and eosin or by Masson's

trichrome method (fig. 15), especially when cut serially. In such slides we could see that these ampullar and beadlike dilatations were directly continuous with adjacent normal stretches of capillary and precapillary channels and that their walls did not differ from the walls of other capillaries and precapillaries (fig. 15). The ampullae are lined with

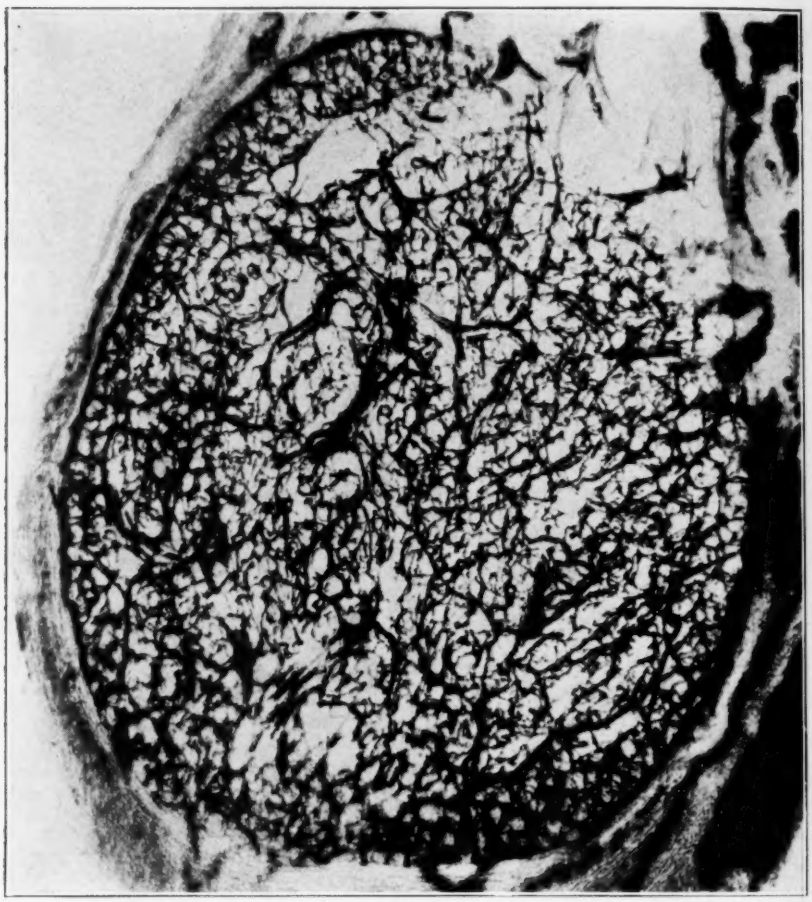

Fig. 11.—Photomicrograph of a lumbar spinal ganglion of a newborn human infant. Note the occasional slight irregularity in caliber of the capillary bed. Benzidine stain; × 45.

endothelium which is directly continuous with the lining of the remainder of the capillary or precapillary channel.

In the spinal ganglia of the adult cat an occasional similar beadlike or ampullar dilatation was seen, however not as frequently as in man (fig. 16).

The significance of these ampullar dilatations is of great interest. They occur only in the gray matter, each being about the size of a spinal ganglion cell. They may replace ganglion cells which have disappeared.

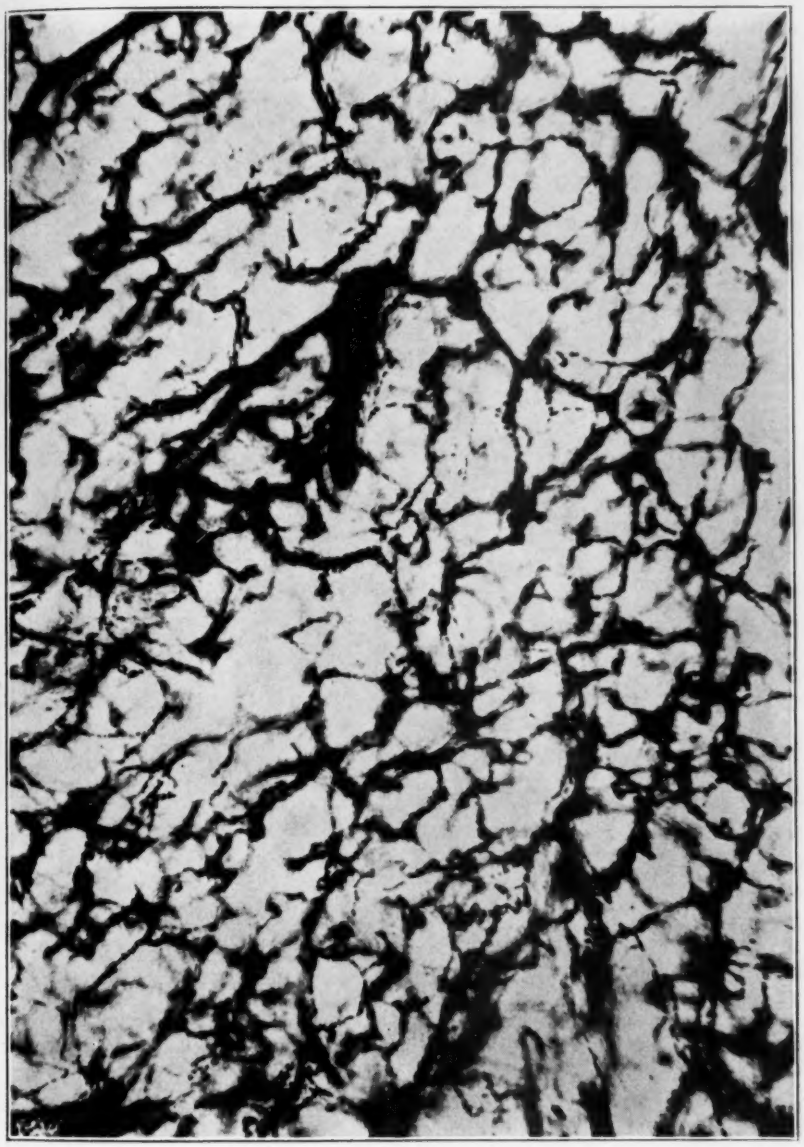

Fig. 12.—Photomicrograph (× 130) of the same specimen as that shown in figure 11. Note the occasional small, beadlike dilatations of the capillary and precapillary vessels, not exceeding three times the diameter of the vessels in the course of which they occur.

Gardner [21b] has made cell counts in thoracic spinal ganglia and found a marked decrease of cells with age. Truex [4] has noted that a great number of cells of the gasserian ganglion of man undergo degeneration or destruction from the third decade of life on. He expressed the opinion that vascular disturbances constitute a factor in this precess.

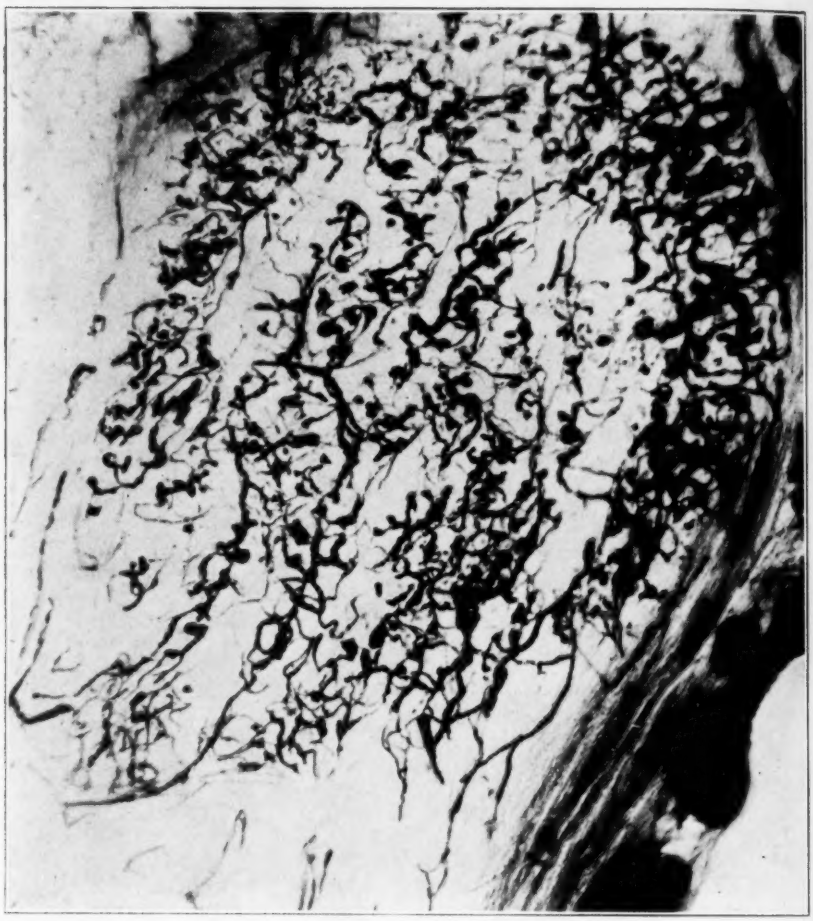

Fig. 13.—Photomicrograph of a thoracic spinal ganglion of a woman aged 29. Note the beadlike and ampullar dilatations of the capillary bed. Benzidine stain; × 42.

He correlated his observations with the clinical studies of Pearson,[22] who demonstrated a gradual decrease in vibratory sensitivity after

21b. Gardner, E.: Decrease in Human Neurons with Age, Anat. Rec. **77**:529-536, 1940.

22. Pearson, G. H. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482-496 (Sept.) 1928.

the third decade of life, and the pathologic investigation of Corbin and Gardner,[23] who demonstrated a decrease in the number of myelinated dorsal root fibers after the third decade. Furthermore, Duncan [24] showed the occurrence of mild degrees of atrophy and

Fig. 14.—Photomicrograph of a thoracic spinal ganglion of a man aged 77. Note the beadlike and ampullar dilatations of the capillary bed. Injection specimen; × 165.

23. Corbin, K. B., and Gardner, E. D.: Decrease in Number of Myelinated Fibers in Human Spinal Roots with Age, Anat. Rec. **68**:63-74, 1937.

24. Duncan, D.: Incidence of Mild Degrees of Atrophy in the Fasciculus Gracillis, Arch. Path. **26**:664-675 (Sept.) 1938.

demyelination in the funiculus gracilis of the cord (which is mainly made up of the central neurites of the spinal ganglion cells) in a great number of adult human beings who had not shown obvious diseases or disturbances of the central nervous system during life.

We cannot definitely decide whether the ampullar dilatations of the capillary bed which we observed or the cellular loss which had been previously observed by other authors is primary. It is conceivable that the vascular ampullae, like local aneurysms, may compress and cause

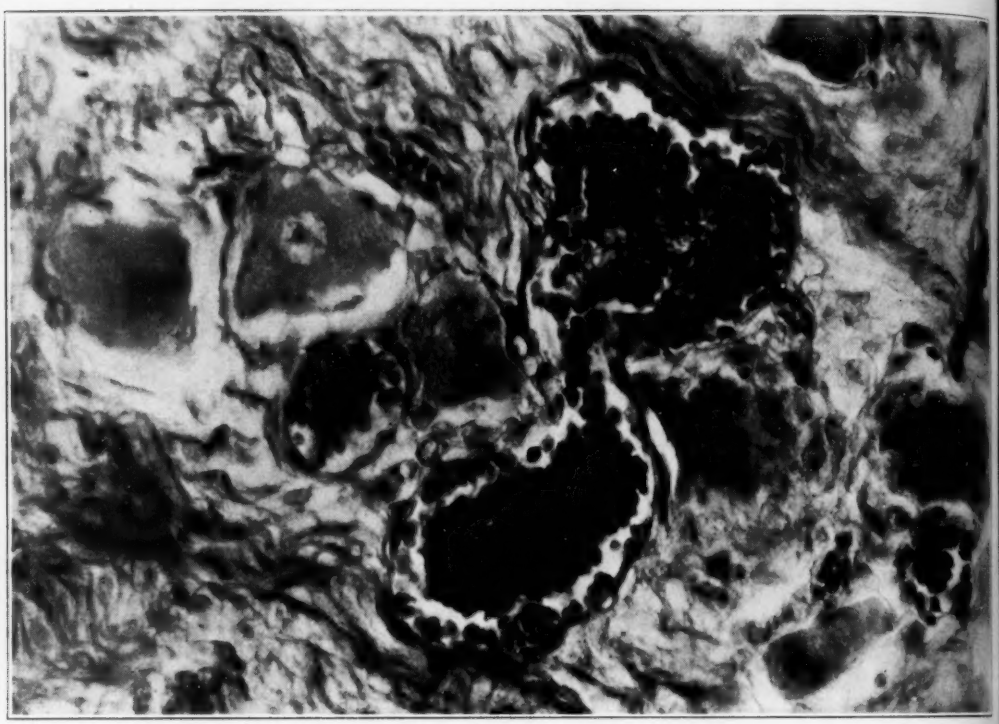

Fig. 15.—Photomicrograph of a thoracic spinal ganglion of a man aged 29 (same case as that from which figure 13 was taken). Note the ampullar dilatations of the vascular bed. The two in the center of the figure are connected by a nondilated stretch of a precapillary. Note the normal endothelial lining and basement membrane of the ampullar dilatations, comparable to those of normal capillaries and precapillaries. Hematoxylin-eosin stain; × 460.

degeneration and destruction of the adjacent neurons. An alternate explanation would be the generally inefficient arterial supply of the spinal ganglia. This inefficiency is exemplified by the fact that most of its arterial vessels do not enter the ganglion in the main direction of the blood stream but branch off at right angles or recurve against the main

direction of blood flow. This has been regarded by Alexander and Putnam [25] as a criterion of inefficient and vulnerable blood supply. It may cause degeneration and destruction of certain ganglion cells, and, secondarily, the adjacent capillary loop may dilate at the site at which a ganglion cell has been lost.

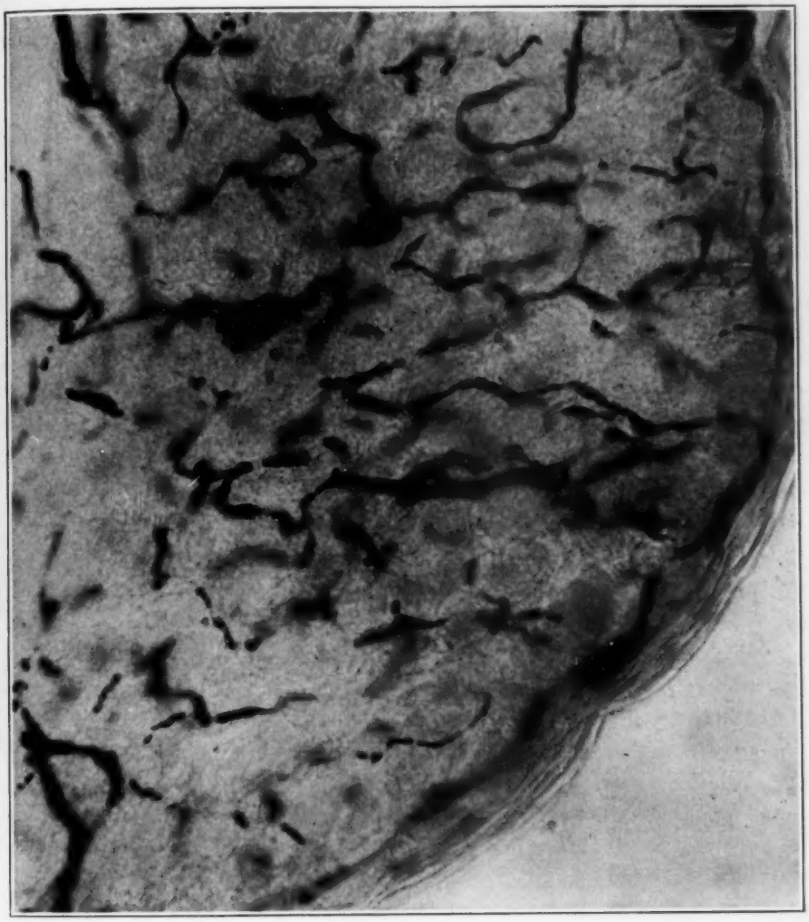

Fig. 16.—Photomicrograph of a thoracic spinal ganglion of an adult cat. Note one ampullar dilatation to the left and above the center of the figure. Benzidine stain; × 170.

SUMMARY AND CONCLUSIONS

1. The spinal ganglia in man and the rhesus monkey receive their blood supply by way of the spinal branches of the dorsal division of each segmental artery, according to a strictly segmental plan.

25. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:471-543, 1938.

2. The veins do not drain segmentally.

3. The arteries originate from several anastomosing branches which are offshoots (side paths) of the posterior (sometimes also the anterior) spinal branch of the segmental (intervertebral) artery, which becomes the respective radicular artery mediad to the ganglion. These offshoots supply the ganglion by piercing its sheath.

4. The arteries enter the ganglion in two groups, one perforating the sheath at the periphery and the other at the poles. These two types of vessels communicate within the ganglion.

5. The veins drain into a rich plexus located around the spinal ganglion and between the dural sheaths of the roots. This plexus is connected with the internal and external vertebral plexuses, with the intervertebral vein and also with the dorsal division of the segmental vein.

6. The capillary bed of the gray matter of the spinal ganglion is dense, comparable to that of the central gray matter, while the capillary bed of the white matter of the spinal ganglion is loose and wide meshed, comparable to that of the central white matter or of the peripheral nerves. This difference suggests that the gray matter of the spinal ganglion has an active metabolism exceeding that of the white matter.

7. The capillaries and small vessels in the gray matter of the spinal ganglia in adult man show frequently beadlike and ampullar dilatations, which are absent in the monkey.

8. Most of the vessels supplying the spinal ganglion originate from the main vascular trunk (the spinal arterial branch) at right angles or by way of recurving arcs, arising off and frequently against the direction of the blood flow in the mother branch. This explains the fact that higher pressure and a longer time are needed to inject the arteries of the spinal ganglion than the spinal and radicular ramifications of the same segmental vessel. If analogy drawn from other, better known parts of the nervous system is permissible, the arterial supply of the spinal ganglia may be considered to be rather vulnerable. There may be some relation between this fact and the frequent occurrence of cellular loss in the spinal ganglia, reduction in the number of posterior root fibers and mild degeneration of the posterior column in an otherwise normal spinal cord after the third decade of life, a concept which is further substantiated by the gradual reduction of sensibility, most readily discernible as a reduction of vibratory sense, from the third decade of life on.

CORRECTIONS

"Intercostal" on page 765, line 15, should read "intervertebral"; "cancerous" on page 773, line 8, should be "cavernous"; on page 774, last line, "onward" should be inserted after "life"; "precess" on page 778, line 5, should read "process"; "spinal" should be inserted before "cord" on page 780, line 1, and "man" on page 780, line 1 of legend for figure 15, should read "woman."

PATHOLOGY OF AMYOTROPHIC LATERAL SCLEROSIS

FIBER ANALYSIS OF THE VENTRAL ROOTS AND PYRAMIDAL TRACTS OF THE SPINAL CORD

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AND

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BOSTON

It has been suggested (Kuré and collaborators [1] and Hechst [2]) that only the large nerve fibers in the ventral roots degenerate in cases of amyotrophic lateral sclerosis and that the small fibers remain intact. Kuré stated that this was true of the pyramidal and rubrospinal tracts as well. As these observations were not supported by measurements and the material was limited, their statements have received little recognition. Marburg [3] expressed the belief that the observations of Kuré and Hechst did not prove that a special fiber system was left intact in the ventral roots, since other investigators had not noted a predominant loss of large fibers in the ventral roots in their cases, and suggested as an alternative that these small fibers were atrophic. Karlström and Wohlfart [4] reported a marked reduction in the number of large nerve fibers in the ventral roots in cases of infantile spinal muscular atrophy, although this was not established by measurements.

In recent years it has become clear that normal ventral spinal roots contain two general classes of nerve fibers, small and large (Kiss and Mihálik,[5] Eccles and Sherrington,[6] Häggqvist [7] and others). The

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1. Kuré, K.: Die vierfache Muskelinnervation, Berlin, Urban & Schwarzenberg, 1931.

2. Hechst, B.: Zur Pathohistologie und Pathogenese der amyotropischen Lateralsklerose, Arch. f. Psychiat. **93**:159-181, 1931.

3. Marburg, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, p. 524.

4. Karlström, F., and Wohlfart, G.: Klinische und histopathologische Studien über infantil spinale Muskelatrophie (Oppenheimsche und Werdnig-Hoffmannsche Krankheit), Acta psychiat. et neurol. **14**:453-488, 1939.

5. Kiss, F., and von Mihálik, P.: Ueber die Zusammensetzung der peripherischen Nerven und den Zusammenhang zwischen Morphologie und Funktion der peripherischen Nervenfasern, Ztschr. f. d. ges. Anat. (Abt. 1) **88**:112-151, 1928.

(Footnotes continued on next page)

relative numbers of fibers of each size in the ventral spinal roots in a normal man were determined by Swensson,[8] and the nerves to the extrinsic muscles of the eye were similarly analyzed by Björkman and Wohlfart,[9] although in the latter studies afferent fibers could not be excluded from the analysis. The remaining cranial nerves exhibit various characteristics, of which some conform to the general plan of the other nerves and some do not (Häggqvist [7c] and Bergstrand [10]).

The purpose of this investigation was to demonstrate by the method of fiber analysis whether one group of nerve fibers in the ventral roots suffers more than another in cases of amyotrophic lateral sclerosis.

MATERIALS AND METHODS

Five cases of amyotrophic lateral sclerosis were chosen for study. In each, tissues from different parts of the central and the peripheral nervous system and the skeletal muscles were studied for the purpose of judging the nature and extent of the pathologic process. The nerve tissues were treated by the usual histologic methods, including myelin stains according to Kultschitzky and Spielmeyer, the Nissl cell stain, hematoxylin and eosin, Holzer's glia stain and sudan III for fat. Frozen sections of muscle tissue were stained for fat, and skeletal muscle, embedded and sectioned in paraffin, was stained by the Mallory connective tissue and the Hansen iron trioxidehematein–acid fuchsin–picric acid method and with iron hematoxylin. Although the cerebral cortex was included in the routine pathologic examination, it will not be described here.

The materials intended for fiber analysis included the ventral and dorsal spinal nerve roots, the spinal cord, the brain stem and the peripheral nerves. As suggested by Häggqvist,[7a] the specimens were fixed in a 10 per cent concentration of solution of formaldehyde, U. S. P., placed in 5 per cent potassium bichromate for two to three weeks, embedded and sectioned in paraffin and stained according to a modified Alzheimer-Mann method (methyl blue and eosin). In the ventral roots, photographs (magnification 750) were taken of a number of suitable fields and the diameters of all fibers in these fields measured. For the purpose of control, the fibers being measured were observed in the microscope. Careful measure-

6. Eccles, J. C., and Sherrington, C.: Numbers and Contraction-Values of Individual Motor-Units Examined in Some Muscles of Limb, Proc. Roy. Soc., London, s.B **106**:326-357, 1930.

7. Häggqvist, G.: (*a*) Analyse der Faserverteilung in einem Rückenmarksquerschnitt, Ztschr. f. mikr.-anat. Forsch. **39**:1-34, 1936; (*b*) Faseranalytische Studien über die Pyramidenbahn, Acta psychiat. et neurol. **12**:457-466, 1937; (*c*) Zur Kenntnis einer doppelten cerebrospinalen Innervation der Skeletmuskeln, Ztschr. f. mikr.-anat. Forsch. **43**:491-508, 1938.

8. Swensson, Å.: Ueber die Kaliberverhältnisse in den vorderen Rückenmarkswurzeln beim Menschen, Ztschr. f. mikr.-anat. Forsch. **44**:187-206, 1938.

9. Björkman, A., and Wohlfart, G.: Faseranalyse der Nn. oculomotorius, trochlearis und abducens des Menschen und des N. abducens verschiedener Tiere, Ztschr. f. mikr.-anat. Forsch. **39**:631-647, 1936.

10. Bergstrand, C. G.: Zur Morphologie der quergestreiften Ringbinden, Ztschr. f. mikr.-anat. Forsch. **44**:45-55, 1938.

ments were not performed on the dorsal spinal roots because suitable normal control values for them were not available. We had planned to analyze the fibers of the pyramidal tracts as Häggqvist did in normal and in a few pathologic cases, but this proved impractical because the nerve fibers in these areas were greatly distorted and obscured by glial tissue. For this reason the diameters of the remaining fibers in the pyramidal tracts were calculated roughly.

The results of the present investigation have been plotted graphically (figs. 3, 5, 6, 9 and 10), the fiber sizes being marked on the abscissas and the numbers of fibers (expressed as percentages of the total) on the ordinates. The detailed results of these studies are presented in the table. For comparison, Swensson's normal values have also been plotted (fig. 1). In sections stained by the Alzheimer-Mann technic many of the unmyelinated fibers of less than 2 microns in diameter and a few of the very small myelinated fibers are not recognized and escape analysis. In the present investigation, however, this can be of little significance, since the large fibers suffered most.

Results of Fiber Analysis of Ventral Spinal Roots *

Spinal cord segment		Case 1				Case 2	Case 3		Case 4				Case 5	
		C_5	T_4	T_{11}	L_2	C_1	C_7	L_2	C_5	C_8	L_2	L_4	T_8	L_2
Diameter of Fibers in Microns	1-2	12.8	8.6	6.1	0.6	....	....	1.1	....	....	....	....	4.3	....
	2-3	16.8	48.0	18.1	23.5	17.7	31.0	11.1	30.9	20.0	15.3	30.0	39.0	31.3
	3-4	14.0	30.8	33.6	24.0	17.1	21.0	11.8	18.4	15.0	21.5	23.0	32.7	32.7
	4-5	21.1	8.5	24.8	26.2	24.2	19.7	28.2	18.7	35.3	33.3	20.0	17.7	28.7
	5-6	12.8	1.3	7.2	8.2	5.1	2.3	17.3	5.1	11.1	10.0	2.6	4.0	1.7
	6-7	11.8	0.6	6.1	9.1	9.5	7.0	12.4	7.1	4.3	10.0	2.6	0.7	2.0
	7-8	4.8	0.5	1.1	1.2	2.0	1.3	2.2	0.2	0.3	1.1	1.8	0.3	0.7
	8-9	2.8	0.5	0.2	1.3	3.7	5.7	3.1	1.1	3.0	2.6	4.4	0.3	0.3
	9-10	2.0	0.2	0.2	...	3.6	1.3	0.4	1.9	4.3	2.0	3.3	0.3	1.0
	10-11	0.6	...	0.4	1.1	2.6	6.3	0.9	3.1	1.7	2.0	7.0	0.7	0.3
	11-12	...	0.2	0.6	...	0.2	1.0	0.7	1.1	1.0	...	1.4	...	0.7
	12-13	...	0.2	1.1	1.7	5.2	0.3	2.2	3.1	1.0	0.6	1.4	...	...
	13-14	...	...	0.4	0.6	5.0	2.3	1.6	2.7	1.7	...	0.7	...	0.3
	14-15	...	...	...	0.2	2.0	0.7	3.4	2.0	0.3	0.2	1.4	...	0.3
	15-16	...	...	...	1.7	1.6	0.3	3.6	4.7	0.6	0.2	...	...	...

The figures express the relative percentages of the fibers of each size.

OBSERVATIONS

CASE 1.—G. A., a 15 year old boy, entered the hospital on May 26, 1939. There was no known hereditary tendency to nervous disease. His mother died of pulmonary tuberculosis. Except for pleurisy at the age of 4 years, the patient's health had been sound, and his development had been normal. He had noted progressive weakness of both arms for approximately one year and of both legs for several months. His general physical condition had been fair. When admitted to the hospital there were marked atrophy and paresis of the muscles of the upper extremities and shoulder girdle, paresis of the sternocleidomastoid muscles and slight atrophy and moderate paresis of the muscles of the lower extremities. There were no visible fibrillary twitchings. Sensibility was normal. The tendon reflexes were diminished in the upper extremities and normal in the lower, and the plantar responses were normal. There was muscular hypotonia of all the extremities. Disturbances of speech or atrophy of the tongue was not noted at any time. Combined cisternal and lumbar puncture with optical registration showed no block. A slight increase was noted in the protein content of the cerebrospinal fluid but none in the number of cells. Biopsy specimens of muscle from the left forearm and the left thigh taken on the eleventh day in the hospital revealed "marked

muscular atrophy of a type characteristic of disease of the anterior horn cells, or possibly of the peripheral nerves." The disease progressed rapidly, and complete paralysis of all extremities developed. In the middle of August the muscles of the thorax and diaphragm became affected, and the patient died on Aug. 26, 1939.

Macroscopic Examination.—The ventral spinal roots were atrophied.

Microscopic Examination.—Myelin preparations from representative levels of the spinal cord, medulla oblongata, pons and midbrain revealed marked degeneration in the corticospinal tracts, most evident in the cervical and thoracic regions. The rest of the anterolateral funiculus of the spinal cord was only slightly affected,

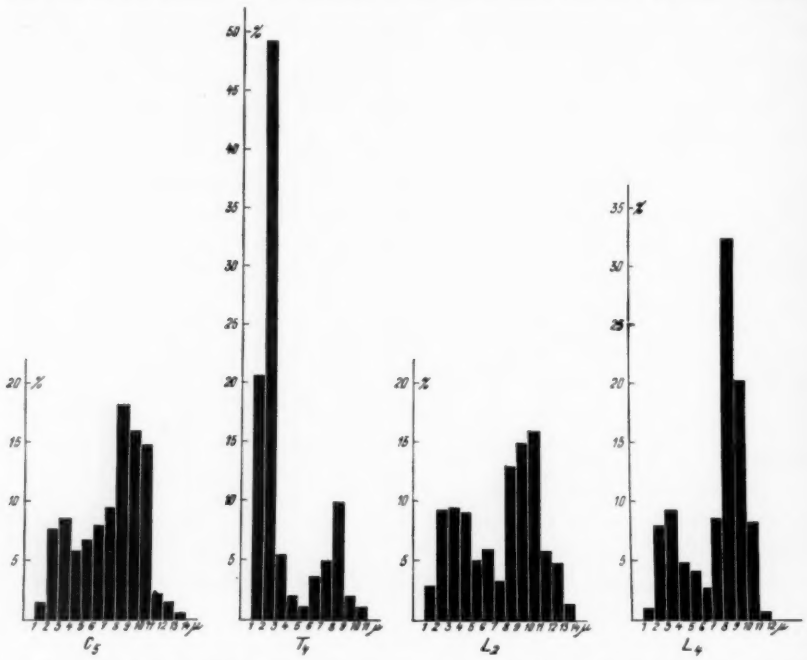

Fig. 1.—Graphs in Swensson's normal case, showing results of fiber analysis of the ventral roots from the fifth cervical, fourth thoracic and second and fourth lumbar segments. Note the preponderance of large fibers, except in the thoracic region (fourth thoracic segment).

and the posterior funiculus was normal. Stains for fat showed a moderate number of fat-laden cells in the cervical and thoracic regions and only a few in the lumbar region. Gliosis was slight in the corticospinal tract areas at all levels. The number of ventral horn motor cells was greatly reduced throughout the spinal cord, and many of those remaining showed fatty degeneration and tigrolysis. In the cervical region only a few small nerve cells remained to occupy the medial part of the anterior horn, and in the thoracic region the few remaining small cells were scattered. In the lumbar region a few large cells remained in the medial part of the ventral gray column. In the lumbar region a few ventral horn cells showed peculiar-shaped intracellular bodies. They varied in size and shape, were homogeneous and weakly basophilic but did not take the usual fat stains. Frequently

they appeared like coagulated fluid. No pathologic changes or decrease in numbers of the nerve cells of the cranial nerve nuclei was evident.

Fiber Analysis.—Fiber counts were carried out on the ventral roots of the fifth cervical, fourth and eleventh thoracic and second lumbar segments of the spinal cord. Corresponding dorsal roots were examined but not analyzed in detail; in all respects these appeared normal. There was a moderate increase in connective tissue in the ventral roots at all levels, especially the fifth cervical, but this did not hinder fiber measurements. Figure 2 *A* and *B* shows typical areas included for the fiber analysis from the ventral roots of the fifth cervical and the eleventh thoracic segments, respectively.

The results of analysis of the four ventral roots previously mentioned are shown graphically in figure 3. These can be compared with Swensson's normal values (fig. 1). As the distribution of fiber sizes between the second and the twelfth thoracic root is practically the same, the values for only one of these roots (the fourth thoracic) from Swensson's study have been included for comparison. It is evident from the diagrams that a tremendous reduction in the number of large nerve fibers has taken place. It cannot be said that the small fibers were unaffected, as total counts were not made, but certainly they suffered relatively little. The greatest apparent reduction in large fibers occurred in the fifth cervical and second lumbar roots, for here the large fibers are more numerous normally. In the ventral spinal roots of the fourth and eleventh thoracic segments the smaller fibers are more numerous normally because of the large number of thin preganglionic sympathetic fibers which they contain, but even here the large fibers have unmistakably been greatly reduced in number. If one arbitrarily considers the fibers above 7 microns in diameter as large and those below this size as small, then, on the basis of Swensson's normal values, the number of large fibers in the ventral spinal root of the fifth cervical segment was reduced from a normal 62.4 per cent to 10.2 per cent; those in the fourth thoracic ventral root from 21.4 to 2.2 per cent; those in the eleventh thoracic root from 19 to 4 per cent, and those in the second lumbar root from 59 to 7.8 per cent.

The pyramidal tract fibers were observed at four different levels of the spinal cord: the fifth cervical, the fifth thoracic, the eleventh thoracic and the second lumbar. In sections from the fifth cervical segment there was pronounced loss of large fibers from the lateral and anterior pyramidal tract areas. Only a few fibers reached a diameter of 15 to 18 microns, and even fibers from 10 to 15 microns in diameter were scanty as compared with those in normal preparations. The smaller fibers appeared relatively intact, although judgment on this matter was difficult because of the marked increase in glial tissue. All other areas of the spinal cord appeared normal. Sections from the other levels of the spinal cord had a similar appearance.

Case 2.—Miss E. B. (whose case was published as case XI in a previous paper [11]), a 28 year old seamstress, entered the hospital for the first time on Dec. 7, 1931. Her history and heredity were noncontributory. In 1928 she had observed paresthesia, weakness and muscular atrophy of the left hand, and in 1929 similar disturbances appeared in the right hand. In the summer of 1931 she had difficulty in talking and swallowing. On admission to the hospital her general physical condition was poor. There were marked atrophy, paresis and

11. Wohlfart, S., and Wohlfart, G.: Mikroskopische Untersuchungen an progressiven Muskelatrophien unter besonderer Rücksichtnahme auf Rückenmarks- und Muskelbefunde, Acta med. Scandinav., 1935, supp. 63, pp. 1-137.

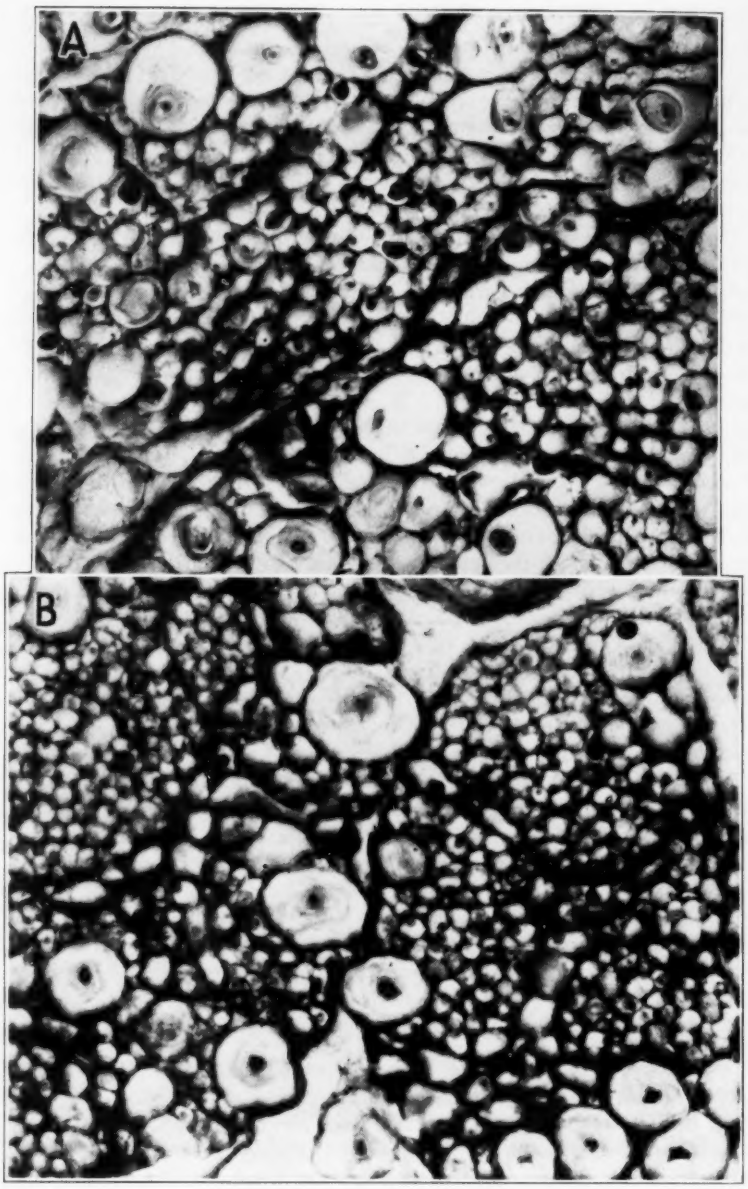

Fig. 2 (case 1).—*A*, ventral root from the fifth cervical segment (× 750). Note marked loss of large fibers and relatively normal-appearing small fibers.

B, ventral root from the eleventh thoracic segment (× 750). Note marked loss of large fibers and relatively normal-appearing small fibers.

fibrillary twitchings of the upper extremities, spasticity of the lower extremities and paresis of the lips, tongue and sternocleidomastoid muscles. Atrophy and fibrillary twitchings of the tongue and difficulty with speech were also present. All forms of sensibility were normal. During the summer of 1932 paresis of the masticatory muscles and atrophy of the muscles of the upper and lower extremities increased, with the result that the patient was bedridden and completely helpless. In the autumn of 1932, when she returned to the neurologic clinic, her general condition was much worse. She had difficulty in swallowing and tachycardia. Slight pyelocystitis developed, and she died suddenly, on Feb. 15, 1933.

Microscopic Study.—There was marked reduction, chiefly in the large anterior horn cells; this was most pronounced in the lateral parts of the cervical and

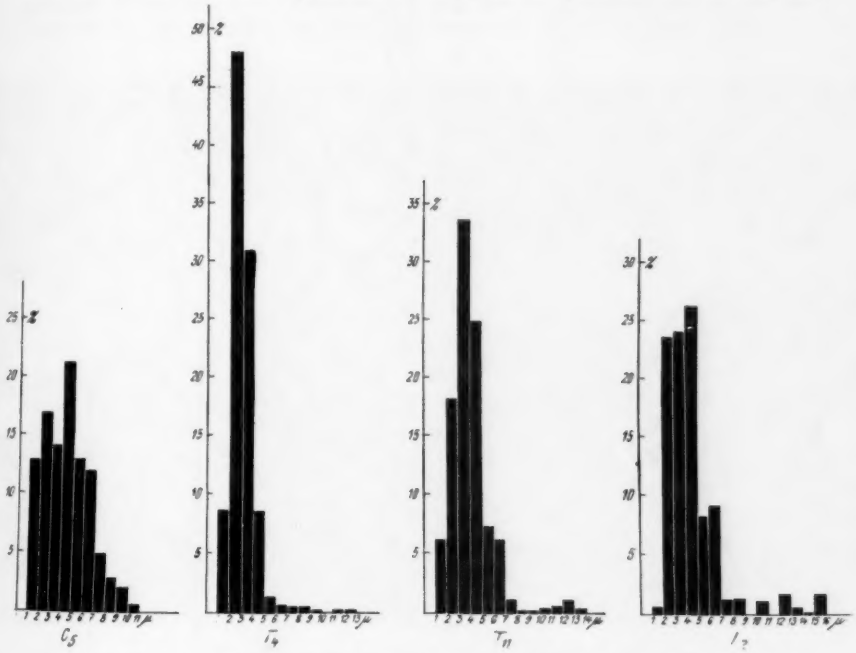

Fig. 3 (case 1).—Results of analysis of the ventral roots from the fifth cervical, fourth and eleventh thoracic and second lumbar segments.

lumbar enlargements. The cells of the rest of the spinal cord appeared normal. In the anterior and lateral funiculi, except in the region of the spinocerebellar tracts, there was marked degeneration of myelin with gliosis. This was most pronounced in the region of the pyramidal tracts.

Biopsies of skeletal muscle from the upper portion of the left upper arm and the left forearm showed atrophy of most of the muscle fibers. Here and there could be seen groups of normal or atrophic muscle fibers in typical motor unit arrangement. The connective tissue was increased, but no interstitial cell groups were seen.

Fiber Analysis.—Fiber counts were possible at only one level of the spinal cord, namely, the first cervical. The dorsal root appeared normal, and even the ventral root seemed but slightly affected (fig. 4 *A*). Fiber analysis (fig. 5) showed

probable loss of large fibers; only 25.9 per cent of the fibers were above 7 microns in diameter, as compared with Swensson's normal value of 44.9 per cent. The first cervical segment of the spinal cord showed considerable loss of nerve fibers of all sizes in both the anterior and the lateral funiculus, except in the area of the spinocerebellar tracts. This was most apparent in the area of the lateral pyramidal tract, where only small, disseminated fibers could be seen.

CASE 3.—Miss J. J., a 40 year old female attendant, entered the hospital on Dec. 17, 1936. For more than a year all four of her extremities had become progressively weaker, and for one year talking and swallowing had been difficult. On admission she was found to have advanced bilateral pulmonary tuberculosis. She lay in bed, unable to sit up, and had periodic fits of crying or laughing. There were advanced atrophy and fibrillary twitchings of the muscles of the arms,

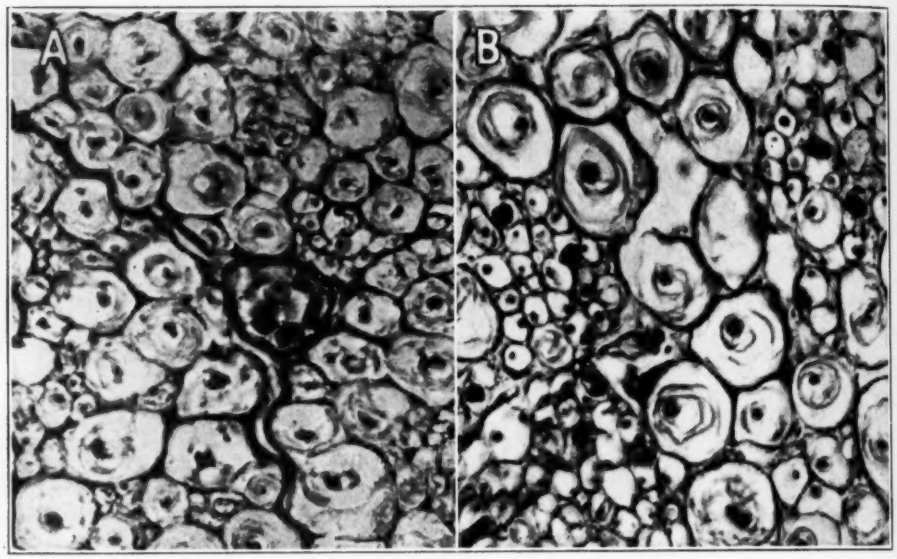

Fig. 4 (case 2).—*A*, ventral root from the first cervical segment (× 750). Loss of large fibers is not readily evident on ordinary microscopic examination (see fig. 5).

B (case 3), ventral root from the second lumbar segment (× 750). Moderate loss of large fibers is readily evident (see fig. 6).

trunk and legs, and she could lift her extremities but a few centimeters off the bed. There was slight but evident muscular hypertonia of the extremities; all muscular reflexes of the extremities were hyperactive, and plantar stimulation produced bilateral extensor responses. Marked atrophy and fibrillary twitchings were present in the tongue. The patient died on Dec. 20, 1936.

Macroscopic Examination.—The ventral spinal roots were slightly atrophic.

Microscopic Examination.—There was slight degeneration of the entire anterolateral funiculus, especially in the lateral and the anterior pyramidal tract. This was more evident on one side. The pyramidal tracts in the brain stem and the

peripheral portion of the spinal cord in the transitional zone between the anterior and the lateral funiculus also showed degeneration. Sections stained for fat revealed many perivascularly arranged, fat-laden cells in the degenerated areas, especially in the pyramidal tracts of the cervical region. There was but slight gliosis. The number of nerve cells in the anterior horn was greatly decreased, especially the large cells in the cervical and thoracic regions. In the lumbar portion of the spinal cord the loss of large cells was less. In the rest of the spinal cord the nerve

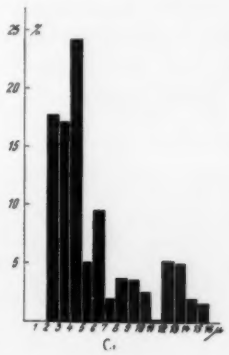

Fig. 5 (case 2).—Results of analysis of the ventral roots from the first cervical segment.

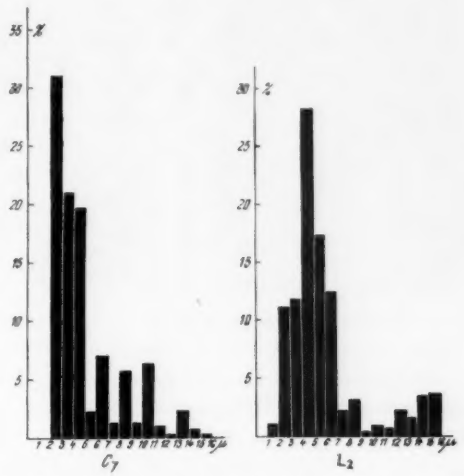

Fig. 6 (case 3).—Results of analysis of the ventral roots from the seventh cervical and second lumbar segments.

cells were normal or showed slight pathologic changes (tigrolysis and pigment atrophy). There was slight gliosis in the anterior horn. Marked loss of nerve cells in the nucleus of the twelfth cranial nerve and slight cellular degeneration in the nucleus ambiguus were noted bilaterally.

Tissue from the tibialis anterior muscle showed mild atrophy of most muscle fibers, with here and there groups of normal-sized fibers in motor unit arrangement. The intramuscular nerve fasciculi, especially the larger ones, showed marked loss

of nerve fibers. Muscle spindles and connective tissue were normal. In the sternohyoid muscle similar, although less marked, changes were present.

Fiber Analysis.—Fiber counts were carried out on the ventral spinal roots from the seventh cervical and the second lumbar segment (fig. 4 *B*). As can be seen in figure 6, the large fibers were markedly reduced in number—in the seventh cervical segment from a normal 67.2 per cent (Swensson) to 19.2 per cent and in the second lumbar segment from 59 to 18.1 per cent. The dorsal roots appeared normal. The upper and lower cervical, upper and lower thoracic and middle lumber segments of the spinal cord were studied. There was loss of large fibers in the pyramidal tract areas (fig. 7 *B*), but nerve fibers of less than 5 to 6 microns in diameter were largely spared (compare the normal-appearing spinocerebellar tract area in figure 7 *A*).

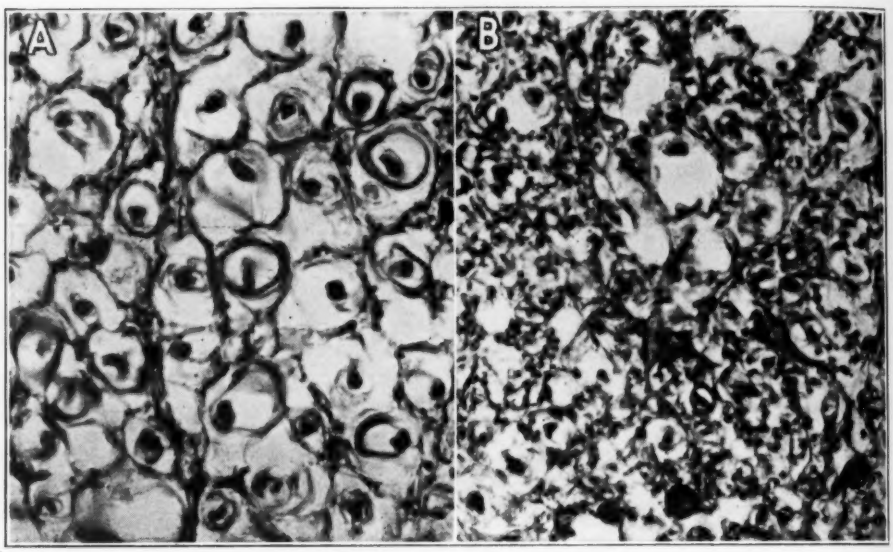

Fig. 7 (case 3).—*A*, spinocerebellar tract areas, lower thoracic level (× 750). Note the large number of large fibers. Compare with *B*.

B, lateral pyramidal tract area, lower thoracic level (× 750). Note evident reduction in the number of large fibers. Compare with *A*.

Case 4.—Mrs. T. N., a 52 year old housewife, entered the hospital on April 27, 1939 complaining of weakness of the legs for eighteen months, especially on the right, weakness and atrophy of both hands for one year and difficulty in talking and swallowing for the last few months. Her history and heredity were noncontributory. On admission her general physical condition was very poor. There was moderate atrophy of the muscles of all the extremities, especially of the forearms and lower portions of the legs, and the muscles of the hands were extremely atrophic. There were mild fibrillary twitchings of the muscles of the extremities, marked fibrillary twitching of the tongue and pronounced atrophy of the tongue. The sternocleidomastoid muscles were weak. The tendon reflexes were slightly hyperactive in the upper extremities and normal in the lower extremities. All

plantar responses were normal. There was no muscular hypertonus. Speech was dysarthric. The cerebrospinal fluid was normal. Sensibility was entirely normal. On the sixteenth day in the hospital biopsy of tissue from the right anterior tibial muscle showed "marked muscular atrophy of the type characteristic of degeneration of the anterior horn cells." Apparent paralysis of the diaphragm developed, and the patient died on May 21, 1939.

Macroscopic Examination.—Nothing pathologic was noted.

Microscopic Examination.—The number of ventral horn cells, especially the large ones in the cervical region, was reduced. Many of the remaining cells exhibited fatty degeneration, and here and there neuronophagia was observed. In the cervical and thoracic regions there was very slight degeneration of the lateral and anterior pyramidal tracts, and in the lumbar region of the spinal cord the white matter appeared normal. There was slight degeneration also in the transitional zone between the anterior and the lateral funiculus, at the periphery of the

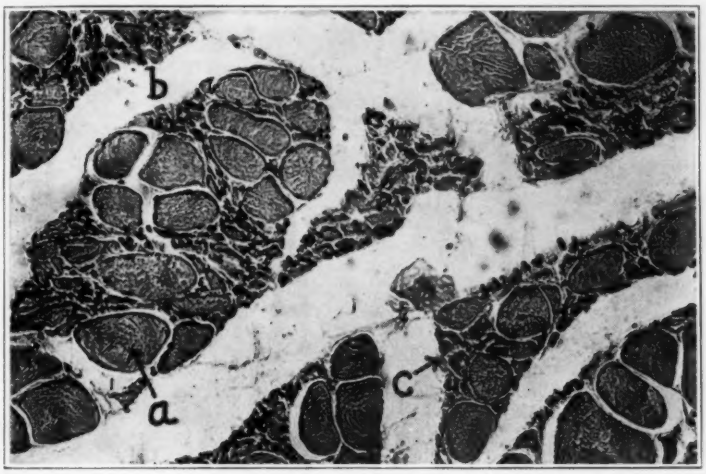

Fig. 8.—Cross section of abdominal muscle fibers, showing typical atrophy of the spinal type (× 200). Note normal-sized fiber at *a*, moderately atrophic fibers at *b* and markedly atrophic fibers at *c*.

spinal cord. In the medulla oblongata and pons there were slight degeneration of the pyramidal tracts and pronounced degeneration of the nerve cells in the nucleus of the twelfth cranial nerve bilaterally.

Skeletal muscle from the extremities and the abdominal muscles, the pectoralis major and the diaphragm showed to a greater or less extent the typical picture of spinal muscular atrophy (fig. 8); bundles of normal fibers were mixed with other bundles of atrophic fibers. No hypertrophic fibers were present, and there was only a slight increase in the interstitial connective tissue. The muscle spindles seemed intact. The external rectus muscle of one eye appeared normal.

Fiber Analysis.—Spinal roots from the fifth and sixth cervical, the second and sixth thoracic and the second and fourth lumbar segments of the cord were studied. There appeared to be considerable loss of large nerve fibers in all the ventral roots, whereas the small fibers seemed normal. All the dorsal roots appeared

normal. The composition of the ventral roots from the fifth and sixth cervical and the second and fourth lumbar segments is shown in figure 9. In the fifth cervical segment 19.9 per cent of the fibers were more than 7 microns in diameter, as compared with Swensson's normal value of 62.4 per cent, and in the sixth cervical segment a similar distribution was evident; 13.9 per cent of the fibers were above 7 microns in diameter, as against Swensson's normal value of 50.5 per cent. The sections from the ventral roots of the second and sixth thoracic segments were technically not satisfactory for accurate fiber analysis. In both roots there was evident loss of large fibers, especially in the second thoracic, whereas the small fibers seemed normal. In the second thoracic root only a few fibers reached the diameter of 15 microns, whereas some fibers in the sixth thoracic root were evidently swollen and had reached a diameter of 20 microns or more. (In his normal case Swensson found few fibers in the thoracic region larger than 12 microns.) In the ventral spinal root of the second lumbar segment (fig. 9) most of the

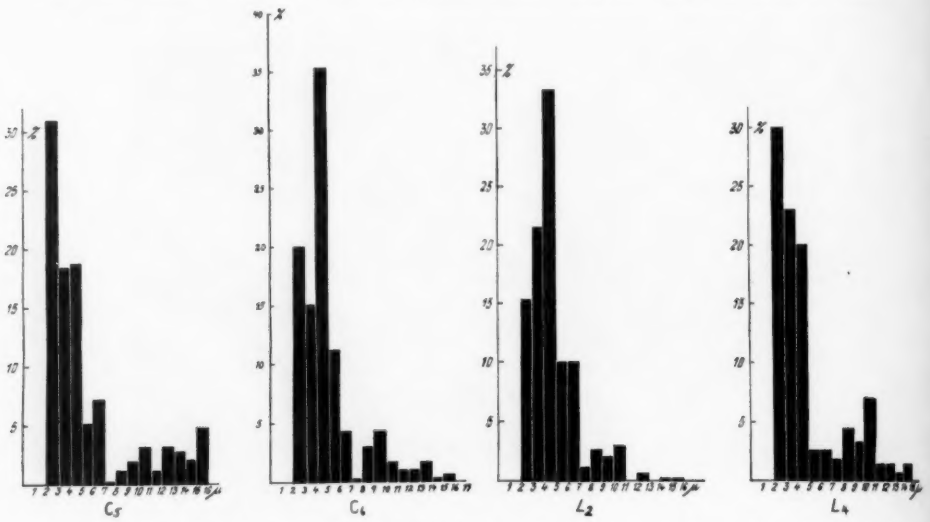

Fig. 9 (case 4).—Results of analysis of the ventral roots from the fifth and sixth cervical and the second and fourth lumbar segments.

large fibers were absent. Only 9.6 per cent were above 7 microns in diameter, whereas Swensson found 59 per cent, but in the ventral root from the fourth lumbar segment the large fibers were relatively more numerous, namely, 21.4 per per cent; Swensson's corresponding normal value was 69.9 per cent.

Sections of the spinal cord from the second and sixth cervical, the second and sixth thoracic and the second and fifth lumbar segments were studied. At all levels there was moderate diffuse loss of nerve fibers in the lateral funiculus, except in the areas occupied by the spinocerebellar tracts. The anterior and posterior funiculi appeared normal. It could not be decided which size fibers had suffered the most in the lateral funiculus, and an increase in glial tissue made the sections unsatisfactory for fiber analysis.

Case 5.—Mr. E. E., a 52 year old official, entered the hospital on Nov. 23, 1937. His history and heredity were noncontributory. In 1931 the patient observed

twitchings in the right biceps muscle. During the following years this spread to the entire musculature of the right and left arms and was accompanied by progressive atrophy of these muscles. Since 1936 increased twitchings and atrophy of the muscles of the lower extremities, the abdomen and the back had appeared. During the last few months the patient had had difficulty in talking and swallowing. In May, June, September and November 1937, the patient received roentgen treatment to different parts of the spinal cord. On admission to the hospital his general physical condition was poor. There were marked generalized muscular atrophy of the extremities and body and numerous fibrillary twitchings in all affected muscles. No disturbances of the ocular, masticatory or facial muscles were noted. Slight paresis of the trapezius muscle was evident; there was no visible atrophy of the tongue and no muscular hypertonus. Tendon reflexes were generally diminished. All plantar responses were normal, sensibility was normal and speech was dysarthric. During his stay in the hospital increasing generalized atrophy and difficulty

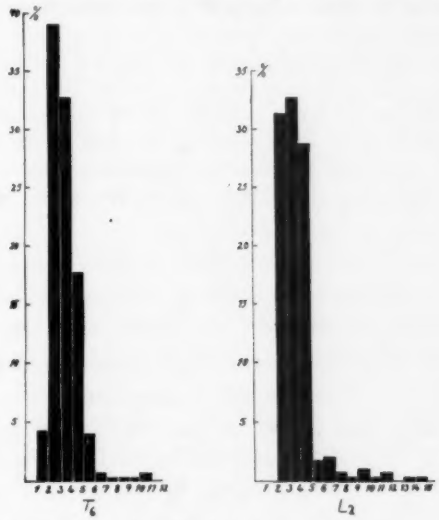

Fig. 10 (case 5).—Results of analysis of the ventral roots from the sixth thoracic and second lumbar segments.

with swallowing developed. On March 7, 1938 the patient had an attack of respiratory difficulty and died.

Microscopic Examination.—Sections revealed moderate degeneration of myelin in the lateral and anterior pyramidal tract areas of the spinal cord, especially on the right side. In the thoracic region on the right side there was slight but evident degeneration of the peripheral part of the spinal cord in the transitional zone between the anterior and the lateral funiculus. Nissl stains revealed nearly complete destruction of the large nerve cells of the ventral horn, especially in the caudal part of the spinal cord. The small ventral horn cells were possibly reduced in number in the lower thoracic and lumbar regions, and a few of them, both in the anterior and in the posterior horn, contained small amounts of fat-staining material. In the brain stem fat stains showed small amounts of fat in the pyramidal tracts of the medulla oblongata but not in more cranial parts of these tracts, and no visible demyelination was noted. The cell stains revealed slight changes in the nucleus ambiguus and the nucleus of the twelfth cranial nerve on both sides.

Fiber Analysis.—Spinal nerve roots were studied from the third and sixth cervical, the sixth thoracic and the second and fifth lumbar segments. All posterior roots appeared normal. In the ventral roots of the third and sixth cervical segments there was pronounced increase in connective tissue, making fiber analysis impossible. There appeared to be moderate loss of large fibers in both roots. It was not possible, however, to decide whether the small fibers were reduced in number because they were to a great extent hidden by interstitial tissue. The results of analysis of the ventral roots of the sixth thoracic and second lumbar segments are shown in figure 10. In these roots the large fibers were greatly reduced in number. In the sixth thoracic root not more than 1.6 per cent of the fibers were more than 7 microns in diameter, as compared with 17.1 per cent in Swensson's case, and in the second lumbar root only 3.6 per cent of the fibers were more than 7 microns in diameter, as compared with 59 per cent in Swensson's case. A satisfactory analysis of the ventral root of the fifth lumbar segment could not be made because of marked increase in interstitial tissue. There appeared to be loss of large fibers in this root, however.

The third and sixth cervical, the sixth thoracic and the second and fifth lumbar segments of the spinal cord were studied. In all parts there was pronounced reduction in the number of large fibers in the lateral pyramidal tract areas, and to some extent even in the anterior funiculi, especially on the right. In the lumbar region possibly a few small fibers in the pyramidal areas were also absent, but there appeared to be no loss of fine fibers in the cervical and thoracic regions.

COMMENT

In each of the 5 cases of amyotrophic lateral sclerosis included in this study pathologic changes associated with this condition were exhibited. There were degeneration of corticospinal fibers in the spinal cord and brain stem, degeneration of ganglion cells in the ventral horns of the spinal cord and nuclei of the cranial nerves, degeneration of peripheral nerve fibers in the ventral roots and changes in spinal musculature of the type seen when anterior horn cells or peripheral nerve fibers degenerate. The posterior columns of the spinal cord appeared normal, as did the spinocerebellar and other peripherally located tracts, with 1 exception. Degeneration was seen in cases 3, 4 and 5 in the transitional, or border, zone between the ventral and the lateral funiculus. This appearance may have been due to the large number of degenerated motor nerve fibers which traverse this zone. It was not possible to state with certainty that the rubrospinal tract was degenerating, as the line of demarcation between it and the corticospinal tract is too indefinite. However, the area of degenerating fibers in the lateral funiculus was large enough to suggest that it was. The nerve cells in the posterior gray substance and the nerve fibers of the dorsal roots appeared normal.

In all of our cases the large nerve fibers in the ventral spinal roots were greatly reduced in number, whereas the small fibers to a very great extent, or perhaps entirely in some cases, remained intact. This

was true at all levels of the spinal cord, but was less distinct in the thoracic and upper lumbar segments. Here the relative number of large fibers is less than elsewhere, because the spinal roots receive many additional small myelinated fibers destined for distribution in the sympathetic nerve chain.[12] A review by Kiss and Mihálik [5] is of interest in this respect. In no ventral roots were all the large fibers destroyed, and a few of those still present were much larger than any of the normal fibers measured by Swensson. This was probably due to swelling, which may occur early in degenerating fibers, or, on the other hand, may represent individual normal variation.

In the spinal cord the large myelinated pyramidal tract fibers appeared to suffer greater damage than did the small fibers. This was especially evident in cases 1, 2 and 5, in which few large fibers remained. In these cases medium and small fibers probably also degenerated. In case 4 degeneration was slight, and not obviously pronounced in any group of fibers. Experience with the ventral roots, however, has shown that one is unable to discern a change in the number of large nerve fibers by ordinary microscopic examination until the reduction is marked. It is probable that the large fibers of the corticospinal tract degenerate before the small, but since the region of this tract is occupied by so many more small than large fibers,[13] the opposite sequence of degeneration could occur and not be readily detected. Recent experiments indicate that many of the fibers in the pyramidal tract area may not arise from the cerebral cortex.[14] Possibly these are the fibers which fail to degenerate, or degenerate late, in cases of amyotrophic lateral sclerosis

Several clinical features were of interest. The first patient noted symptoms at the age of 14 and died less than one year later. Because of the early onset of symptoms and the subsequent rapid progress, diagnosis was uncertain until after the muscle biopsy. A hereditary-familial type of amyotrophic lateral sclerosis with onset before the age of 22 has been described,[15] but this condition usually progresses slowly. The patient in case 3 had periodic bursts of laughter and crying,

12. Gaskell, W. H.: On the Structure, Distribution and Function of the Nerves Which Innervate the Visceral and Vascular Systems, J. Physiol. **7**:1-80, 1886.

13. Lassek, A. M., and Rasmussen, G. L.: The Human Pyramidal Tract, Arch. Neurol. & Psychiat. **42**:872-876 (Nov.) 1939; A Comparative Fiber and Numerical Analysis of the Pyramidal Tract, J. Comp. Neurol. **72**:417-428, 1940. Häggqvist.[7b]

14. Swank, R. L.: The Pyramidal Tract: An Experimental Study of the Corticospinal Tract and Other Components in the Rabbit, Arch. Neurol. & Psychiat. **36**:530-541 (Sept.) 1936. Häggqvist.[7b]

15. von Santha, K.: Ueber die endogen-systematische Natur der amyotrophischen Lateralsklerose, Arch. f. Psychiat. **97**:142-184, 1932. Schaffer, K., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, pp. 605-657. Curschmann, H.: Ueber familiäre amyotrophische Lateralsklerose, Deutsche Ztschr. f. Nervenh. **149**:133-140, 1939.

symptoms which have been studied recently by Davison and Kelman.[16] The presence of another condition, advanced pulmonary tuberculosis, may have been a factor in this case.

In cases 1, 4 and 5 the tendon reflexes were normal or hypotonic and the plantar responses normal. This was probably due to the mildness of the changes in the corticospinal tract in case 4, but in cases 1 and 5 these pathways were severely degenerated. Cases of pseudopolyneuritis with similar symptoms have been reported,[17] and it has been suggested [18] that the signs of degeneration of the pyramidal tracts may be obscured in such cases by extensive damage to the ventral horn cells. This explanation is corroborated by the fact that the large ventral root fibers in cases 1 and 5 were more severely damaged than in any other of our cases. Possibly these fibers are necessary for the production of hypertonus and extensor plantar reflexes.

It is now clear that small myelinated fibers (in addition to the large) are numerous in ventral roots which contain no sympathetic preganglionic fibers. In Swensson's case the upper sacral roots were an exception, but this may have been due to individual variation. According to Eccles and Sherrington,[6] motor nerve fibers may divide many times before reaching their terminations, but still retain their original fiber size characteristics. These investigators expressed the belief that the small fibers innervated small and the large fibers large muscle groups.

Häggqvist [7c] suggested that the small motor nerve fibers arise from small nerve cells in the ventral horns, especially those in the medial part. In experiments on rabbits he succeeded in destroying the large fibers in the ventral roots and the large nerve cells in the ventral gray columns by compressing the abdominal aorta for fifteen to twenty-five minutes. The small cells and fibers remained intact. Our observations suggest similar origins for the large and the small ventral root fibers in human subjects, the large fibers arising from large and the small fibers arising from small ventral horn cells. The observations of Häggqvist and the results of the present study indicate that the small and the large fiber groups in the ventral roots are functionally as well

16. Davison, C., and Kelman, H.: Pathologic Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595-643 (Oct.) 1939.

17. Patrikios, J. S.: Contribution à l'étude des formes cliniques et de l'anatomie pathologique de la sclérose latérale amyotrophique, Thesis, Paris, no. 149, 1918. Foix, M.; Chavany, J. A., and Bascourret: Étude anatomoclinique d'un cas de sclérose latérale amyotrophique à forme pseudo-polynévritique, Rev. neurol. **32**: 822-826, 1925. Wohlfahrt, S.: Die vordere Zentralwindung bei Pyramidenbahnläsionen verschiedener Art; eine histopathologische Untersuchung, Acta med. Scandinav., 1932, supp. 46, pp. 1-235.

18. Ottonello, P.: Sulla sclerosi laterale amiotrofica, Rassegna di studi psichiat. **18**:221, 397 and 557, 1929. Marburg.[3]

as anatomically different. Recent neurophysiologic investigations[19] appear to support this view, inasmuch as the speed of an impulse in a peripheral nerve fiber is greater in large than in small fibers.

Selective degeneration of nerve fibers based on size has also been noted in thiamine-deficient pigeons. In acutely deficient pigeons with opisthotonos the large vestibular nerve fibers are the first to degenerate,[20] and in very chronically deficient pigeons with "locomotor ataxia" the large and long proprioceptive nerve fibers in the peripheral nerves degenerate.[21]

Muscle biopsies have been found helpful for diagnosis in this as well as in other neuromuscular diseases.[22] In the experience of one of us (G. W.), the muscular changes in amyotrophic lateral sclerosis and progressive muscular atrophies are quite characteristic (fig. 8).

CONCLUSION

In 5 cases of amyotrophic lateral sclerosis measurements showed that most of the large nerve fibers in the ventral spinal roots had disappeared, whereas the small fibers appeared normal. The large ventral horn nerve cells suffered a similar fate, the small cells remaining relatively normal. Accurate measurements of the corticospinal tract fibers were made impossible by glial tissue, but it appeared that here the large fibers also suffered the greater damage. All posterior spinal roots appeared normal.

In 2 cases in which bilateral degeneration of the pyramidal tracts was marked muscular hypertonus was not noted, the deep reflexes were normal or hypoactive and extensor plantar responses were absent. In these cases the large fibers in the ventral roots were more extensively damaged than in any of the other cases. It might be inferred from this observation that signs of degeneration of the pyramidal tracts are dependent for their production on the large ventral root fibers.

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19. Erlanger, J., and Gasser, H. S.: The Compound Nature of the Action Current of Nerve as Disclosed by the Cathode Ray Oscillograph, Am. J. Physiol. **70**:624-666, 1924. Erlanger, J.: Interpretation of Action Potential in Cutaneous and Muscle Nerves, ibid. **82**:644-655, 1927. Zotterman, Y.: Action Potentials in the Glosso-Pharyngeal Nerve and in the Corda Tympani, Skandinav. Arch. f. Physiol. **72**:73-77, 1935; Specific Action Potentials in Lingual Nerve of Cat, ibid. **75**:105-120, 1936; A Note on the Relation Between Conduction Rate and Fiber Size in Mammalian Nerves, ibid. **77**:123-128, 1937.

20. Recent observations made in collaboration with Dr. M. Prados, at the Montreal Neurological Institute.

21. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683-702, 1940.

22. Wohlfart, G.: Ueber das Vorkommen verschiedener Arten von Muskelfasern in der Skelettmuskulatur des Menschen und einiger Säugetiere, Acta psychiat. et neurol., 1937, supp. 12, pp. 1-119.

STUDIES IN DISEASES OF MUSCLE

X. PROSTIGMINE AND PHYSOSTIGMINE IN THE TREATMENT OF MYASTHENIA GRAVIS

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With the Technical Assistance of Mr. W. E. Bartels

NEW YORK

The discovery by Walker [1] that the administration of prostigmine and physostigmine to patients with myasthenia gravis is followed by definite improvement in muscular function was an important advance in the management of this condition. Both prostigmine and physostigmine depress the activity of the choline esterase and thereby decrease the rate of hydrolysis of acetylcholine, which, according to the studies of Dale and his colleagues,[2] is liberated when cholinergic nerves are stimulated. The administration of prostigmine or physostigmine, therefore, produces effects similar to those seen after stimulation of cholinergic nerves. The chemical reactions involved in the liberation of acetylcholine when cholinergic nerves are stimulated and the effect of prostigmine and physostigmine on the destruction of acetylcholine are shown in figure 1.

The fact that prostigmine and, to a less extent, physostigmine often have a dramatic effect on the muscular symptoms has led some workers to believe that the defect in myasthenia gravis is either a subnormal production of acetylcholine or an increased activity of the choline esterase (Pritchard,[3] Hamill,[4] Hicks and Mackay,[5] McGeorge,[6] Stedman and

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From the Departments of Medicine, Psychiatry and Pharmacology, Cornell University Medical College, the Russell Sage Institute of Pathology and the New York Hospital.

1. Walker, M. B.: Case Showing the Effect of Prostigmin on Myasthenia Gravis, Proc. Roy. Soc. Med. **28**:759, 1935.

2. Dale, H. H., and Feldberg, W.: The Chemical Transmission of Secretory Impulses to the Sweat Glands of the Cat, J. Physiol. **82**:121, 1934; The Chemical Transmitter of Vagus Effects to the Stomach, ibid. **81**:320, 1934. Brown, G. L.; Dale, H. H., and Feldberg, W.: Reactions of Normal Mammalian Muscle to Acetylcholine and to Eserine, ibid. **87**:394, 1936. Dale, H. H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Motor Nerve Endings, ibid. **86**:353, 1936. Dale, H. H.: Transmission of Nervous Effects by Acetylcholine, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 229.

3. Pritchard, E. A. B.: The Use of "Prostigmin" in the Treatment of Myasthenia Gravis, Lancet **1**:432, 1935.

Russell,[7] Kennedy and Wolf,[8] Säker[9] and Harvey[10]). The muscular disability in myasthenia gravis resembles, at least superficially, the disturbance seen in animals poisoned with curare. The resemblance is increased by the antagonistic action of prostigmine to curare (Aeschlimann and Reinert[11] and Briscoe[12]) and by the therapeutic effect of prostigmine in cases of myasthenia gravis. But, further than this, experimental evidence of the nature of the defect in myasthenia gravis is lacking. On the other hand, all the available evidence indicates that the activity of the choline esterase in this condition is not unusual. McGeorge,[6] Milhorat[13] and Poncher and Wade[14] found the serum esterase activity in patients with myasthenia gravis to be of the same order as that seen in patients without this condition. The formulation that the esterase activity in myasthenia gravis is neither greater nor less than in the normal condition assumes, of course, a relation between the esterase activity in the serum and that at the nerve endings, since the determination of the esterase activity has been made on the serum. While no direct evidence of this relation is available at present, it appears highly probable that such a relation exists (Milhorat[13]).

The use of prostigmine in the treatment of patients with myasthenia gravis has been the subject of many reports (Walker,[1] Pritchard,[3]

4. Hamill, P.: Further Uses of Prostigmin, Lancet **1**:575, 1935.

5. Hicks, C. S., and Mackay, M. E.: The Choline-Esterase Activity of Blood Serum from Two Cases of Myasthenia Gravis, Australian J. Exper. Biol. & M. Sc. **14**:275, 1936.

6. McGeorge, M.: Choline Esterase Activity in Disease, with Special Reference to Myasthenia Gravis, Lancet **1**:69, 1937.

7. Stedman, E., and Russell, W. R.: The Choline-Esterase Content of Blood in Myasthenia Gravis, Biochem. J. **31**:1987, 1937.

8. Kennedy, F., and Wolf, A.: Experiments with Quinine and Prostigmin in Treatment of Myotonia and Myasthenia, Arch. Neurol. & Psychiat. **37**:68 (Jan.) 1937.

9. Säker, G.: Klinische Untersuchungen zur Frage der Prostigminwirkung bei der Myasthenia gravis, Deutsche Ztschr. f. Nervenh. **146**:138, 1938.

10. Harvey, A. M.: The Mechanism of Action of Quinine in Myotonia and Myasthenia, J. A. M. A. **112**:1562 (April 22) 1939.

11. Aeschlimann, J. A., and Reinert, M.: The Pharmacological Action of Some Analogues of Physostigmine, J. Pharmacol. & Exper. Therap. **43**:413, 1931.

12. Briscoe, G.: The Antagonism Between Curarine and Prostigmin and Its Relation to the Myasthenia Problem, Lancet **1**:469, 1936.

13. Milhorat, A. T.: The Choline-Esterase Activity of the Blood Serum in Disease, J. Clin. Investigation **17**:649, 1938.

14. Poncher, H. G., and Wade, H. W.: Blood Choline Esterase in Myotonia Congenita and Myasthenia Gravis, Arch. Neurol. & Psychiat. **41**:1127 (June) 1939.

Lindsley,[15] Eichenwald,[16] Verbiest,[17] Laurent,[18] Kostakow,[19] Laurent and Walker,[20] Everts,[21] Hicks and Mackay,[5] McGeorge,[6] Winkelman and Moore,[22] Harvey and Whitehill,[23] Tabachnick,[24] Säker [9] and Viets and Schwab [25]). However, knowledge of the action and effects of the drug in this condition still is incomplete and unsatisfactory. Practically all these reports have emphasized the beneficial effects of prostigmine but have failed to discuss the factors limiting the use of the drug in treatment of myasthenia gravis.

Russel [26] and Moore [27] referred to the exacerbation of muscular symptoms that sometimes occurs after large doses of prostigmine have been given, and Tarlau [28] mentioned the diminishing effect of the drug in patients who are seriously ill, but these important questions appear to have been pursued no further. Another subject which has been mentioned briefly by Walker,[29] Briscoe [12] and Krüger and Säker [30] but

15. Lindsley, D. B.: Myographic and Electromyographic Studies of Myasthenia Gravis, Brain **58**:470, 1935.

16. Eichenwald, E.: Zur Behandlung der Myasthenia, Med. Welt **9**:1705, 1935.

17. Verbiest, H.: Prostigmin in Therapy of Myasthenia Gravis, Nederl. tijdschr. v. geneesk. **79**:4372, 1935.

18. Laurent, L. P. E.: Clinical Observations on the Use of Prostigmin in the Treatment of Myasthenia Gravis, Brit. M. J. **1**:463, 1935.

19. Kostakow, S.: Ueber klinische Beobachtungen bei Myasthenia gravis mit Prostigmin (Roche), Deutsche med. Wchnschr. **62**:296, 1936.

20. Laurent, L. P. E., and Walker, M. B.: Oral and Parenteral Administration of Prostigmine and Its Analogues in Myasthenia Gravis, Lancet **1**:1457, 1936.

21. Everts, W. H.: The Treatment of Myasthenia Gravis by the Oral Administration of Prostigmine, Bull. Neurol. Inst. New York **4**:523, 1935.

22. Winkelman, N. W., and Moore, M. T.: Prostigmin in the Treatment of Myasthenia Gravis and Muscular Dystrophy: Results Obtained with Divided Doses, Arch. Neurol. & Psychiat. **37**:237 (Feb.) 1937.

23. Harvey, A. M., and Whitehall, M. R.: Prostigmin as an Aid in the Diagnosis of Myasthenia Gravis, J. A. M. A. **108**:1329 (April 17) 1937.

24. Tabachnick, H.: Myasthenia Gravis: Consideration of Recent Advances and Influence of Pregnancy; Report of Case, J. A. M. A. **110**:884 (March 19) 1938.

25. Viets, H. R., and Schwab, R. S.: The Diagnosis and Treatment of Myasthenia Gravis, with Special Reference to the Use of Prostigmine, J. A. M. A. **113**:559 (Aug. 12) 1939.

26. Russel, C. K., in discussion on Winkelman and Moore.[22]

27. Moore, M. T., in discussion on Winkelman and Moore.[22]

28. Tarlau, M.: Prostigmin in Myasthenia Gravis: Report of Two Cases, J. Nerv. & Ment. Dis. **88**:330, 1938.

29. Walker, M. B.: Treatment of Myasthenia Gravis with Physostigmine, Lancet **1**:1200, 1934; footnote 1.

30. Krüger, E., and Säker, G.: Experimentelle Untersuchungen zur Frage der Prostigminwirkung bei der Myasthenia gravis, Deutsche Ztschr. f. Nervenh. **146**: 154, 1938.

on which no detailed or critical studies heretofore have been made is the comparison of effects of prostigmine and of physostigmine on the muscles and other organs of patients with myasthenia gravis.

While the present investigations have included extensive observations on the use of prostigmine in the management of patients with myasthenia gravis, the main objectives of the study have been the elucidation of the following questions: (1) the difference in the magnitude of the effects of prostigmine and those of physostigmine on voluntary muscle and other structures; (2) the exacerbation of muscular symptoms that occurs in some patients a few hours after the administration of large amounts of prostigmine; (3) the progressive diminution in the therapeutic effects of prostigmine in some patients who are seriously ill with myasthenia gravis; (4) the increase in muscular disability in patients with acute infections and the decreased effect of prostigmine under these conditions, and (5) certain undesirable, but interesting, effects of large doses of

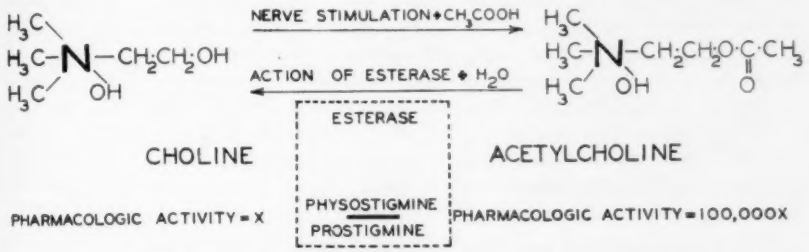

Fig. 1.—Formulation of reactions involved in the production and hydrolysis of acetylcholine. The source of the acetylcholine liberated after cholinergic nerve stimulation is still unknown, but it is probable that acetylcholine is synthesized by acetylation of choline. Choline is found wherever lecithins exist in the body, and the nervous system contains large amounts of these substances. The source of the acetyl radical probably is acetic acid, since this acid is liberated when acetylcholine is hydrolyzed by the enzyme choline esterase. Choline has pharmacologic actions that are qualitatively similar to those of acetylcholine, but these actions are weak. However, the addition of the acetyl radical to form the ester, acetylcholine, increases the pharmacologic activity about 100,000 times (Hunt, R.: J. Pharmacol. & Exper. Therap. **6**:477, 1914-1915). Acetylcholine is reconverted rapidly to the relatively inert choline by the enzyme choline esterase. The inactivation of the esterase by prostigmine or physostigmine decreases the speed of this reaction and produces effects similar to those seen after administration of acetylcholine or after stimulation of cholinergic nerves. The depression of the esterase activity by these drugs is believed by McGeorge [6] to be due to inhibition of the enzyme and not to its destruction, since restoration of esterase activity was observed when the prostigmine was removed by dialysis.

prostigmine. These include auricular fibrillation, temporary stopping of the heart and asthma.

In addition, studies were made on the effect of guanidine, ergotamine tartrate and acetylbetamethylcholine on patients with myasthenia gravis.

MATERIAL AND METHODS

There were 15 patients with myasthenia gravis in the present series; the investigation consisted of long periods of follow-up observations in the outpatient department, in which the effects of oral administration of prostigmine bromide or of other substances were studied, and periods in which the patients were maintained in a special research ward.[31] The choline esterase activity of the serum was determined at frequent intervals. In the case of the patients who were maintained in the research ward these determinations often were made several times during the day. Usually the esterase studies were made at the following times: (*a*) when muscular disability was definite and medication was required; (*b*) at the earliest moment after the administration of prostigmine or physostigmine, when a beneficial effect of the drug on muscular function could be demonstrated, and (*c*) when the therapeutic effect of the drug was at its height. In each instance a careful examination of muscular function was made and the findings were recorded.

The method employed for the determination of the choline esterase activity of the serum was McGeorge's modification[6] of the procedure of Stedman, Stedman and White[32] and was similar to that described in a previous report (Milhorat[13]). The method utilizes the amount of acid liberated in the hydrolysis of acetylcholine by the serum as an index of the activity of the choline esterase. The number of cubic centimeters of one-hundredth normal sodium hydroxide needed to neutralize the acid during a period of twenty minutes is the unit used for expressing the choline esterase activity. The values given in this report have been corrected by subtracting the amount of alkali used in the blank determinations. In each instance simultaneous determinations of the spontaneous cleavage of duplicate samples of acetylcholine substrate were made.

ACTIVITY OF THE SERUM CHOLINE ESTERASE IN MYASTHENIA GRAVIS

Data on the choline esterase activity of the serum in various clinical conditions, including myasthenia gravis, have already been published (Milhorat[13]). These observations have been extended, and up to the present over 150 subjects have been studied. In most instances several determinations of the esterase activity of the serum were made. The data, which are summarized in figure 2, confirm the conclusion made previously that in patients with myasthenia gravis the choline esterase activity of the serum is no different from that observed in subjects without this condition. Moreover, the esterase activity usually was constant over long periods unless the patient was given a drug, such as prostigmine or physostigmine that depresses the esterase activity. The excep-

31. For parenteral administration prostigmine methylsulfate, the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate, was used.

For oral administration prostigmine bromide, the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium bromide, was used.

32. Stedman, E.; Stedman, E., and White, A. C.: A Comparison of the Choline-Esterase Activities of the Blood Sera from Various Species, Biochem. J. **27**:1055, 1933.

tions to this general observation were those cases in which the subject was suffering from severe debilitation. In such instances the esterase activity often changed with the clinical condition of the patient. Repeated observations on 9 patients with myasthenia gravis over periods of as long as two years showed that only minor variations in the activity of the choline esterase occurred, and these could not be correlated with spontaneous changes in muscular symptoms.

PROSTIGMINE IN THE MANAGEMENT OF AMBULATORY PATIENTS

Ten of the patients in the present series were given prostigmine daily for prolonged periods, in several instances over three years. In addition, 3 other patients with myasthenia gravis took prostigmine for periods

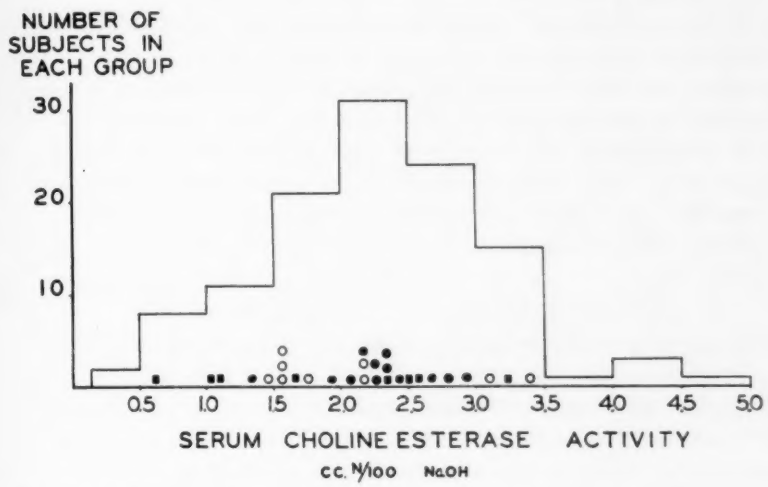

Fig. 2.—Activity of serum choline esterase in 125 patients representing various types of clinical syndromes, including myasthenia gravis. The lines represent the number of patients in the various groups having similar esterase levels. The solid circles represent individual patients with myasthenia gravis; hollow circles, those with rheumatic heart disease, and solid squares, those with chronic nephritis. These are shown to demonstrate that the distribution of the cases of myasthenia gravis in groups representing different levels of esterase activity is the same as that for the two conditions which are unrelated to myasthenia gravis.

of from three weeks to six months, but a remission of symptoms made further medication unnecessary. The experience gained from observing these 13 patients at frequent intervals can be summaried as follows:

1. Prostigmine was of considerable benefit to all patients in whom the muscular weakness and fatigability were only slight or moderate. Often all symptoms of muscular involvement were relieved entirely for periods of from two to three hours after the administration of a single

dose of the drug. Patients more seriously ill with the disease derived definite benefit from the drug, but the improvement in muscular function usually was less than in patients only moderately ill. Not only were larger amounts necessary, but the time required for the muscular effects to appear after the drug had been administered was longer, and the period of clinical improvement induced by the prostigmine was shorter than that in patients in whom the muscular disability was slight or moderate.

2. To all of the ambulatory patients prostigmine bromide was administered orally in the form of tablets containing 15 mg. of the drug. However, ampules of prostigmine methylsulfate for parenteral use were kept on hand by all patients in whom it was considered likely that sudden exacerbation of muscular weakness might develop.

3. Maximal benefit was obtained when the smallest amounts of prostigmine that gave satisfactory effects were used. In several instances in which this dose was exceeded exacerbation of symptoms occurred after the therapeutic effects had subsided. Some patients, when first given prostigmine, took increased amounts of the drug, against the physician's advice. Without exception they obtained increased beneficial effects for a few days but noticed increased muscular fatigability and weakness after this short period of improvement. In a few instances further increases in the dose were necessary. Moreover, some of the patients found that whereas they previously had required no prostigmine in the morning until after arising from bed and dressing, they now found it necessary to take the drug immediately on awakening. As a result all of these patients soon learned to limit the amounts of prostigmine. Many of the patients in the present series voluntarily have reduced the dose to that which gives a moderate effect. The amounts used in most instances did not exceed 5 tablets (15 mg. each) of prostigmine bromide daily, taken orally.

4. The amounts of prostigmine required varied from time to time in most patients as a result of spontaneous changes in the severity of the condition and of factors such as menstruation, infections of the respiratory tract and variations in physical activity. However, in none of these patients was there any evidence of increased tolerance for the drug. Despite the difference in the muscular effects induced by the drug when similar amounts were administered during periods of remission and of exacerbation of symptoms, no difference in the effect of the drug on the esterase activity of the serum could be demonstrated. One patient gave a history of increased muscular weakness when a sedative drug was taken and found it necessary to increase the dosage of prostigmine during this period. Edgeworth [33] previously had observed an unfavorable effect on muscular symptoms when drugs that depress the nervous

33. Edgeworth, H.: Personal communication to the authors.

system were used. A satisfactory explanation for these results is given by the investigation of Koppanyi, Linegar and Dille,[34] who found that the sensitization of the vagus nerve induced by physostigmine is antagonized by barbiturates, and of Crittenden,[35] who observed that a compound of chloral and dextrose (chloralose) and paraldehyde antagonize the secretory response of the pancreas and submaxillary glands to prostigmine and physostigmine.

5. Restriction of activity constituted an important part of the regimen in all instances. Whenever it was possible the patients rested for about an hour in the afternoon.

6. Other therapeutic substances given in addition to prostigmine often were found to be of value. These included ephedrine and aminoacetic acid. Doses of ephedrine sulfate of the order of 7 mg. given two or three times daily were found to be more effective than the large dose of about 25 mg. usually suggested. The larger doses induced tachycardia and headache in some patients and not infrequently had less beneficial effect on the muscular symptoms than the small amounts. Aminoacetic acid was given in amounts of about 20 Gm. daily. This was given in divided doses in fruit juices throughout the day.

7. In addition to the use of drugs, certain general considerations, suggested by Edgeworth,[33] were found to be of value. Each patient was advised to include the following rules in the regimen: (*a*) a judicious effort to avoid respiratory infections, and careful treatment of common colds and other infections of the respiratory tract when they occurred; (*b*) avoidance of excessive exposure to strong and direct sunlight; (*c*) avoidance of sedatives; (*d*) frequent ingestion of small amounts of carbohydrate, and, (*e*) above all, avoidance of excessive muscular activity.

8. The management of the patients included a careful evaluation of all factors influencing muscular function. In all instances of exacerbation of symptoms or those in which prostigmine appeared not to be as effective as previously, examination for any complicating disease was made. Hyperthyroidism, infections, malnutrition, emotional reaction to the disease and many other factors can seriously alter the course of myasthenia gravis. The observations made in the present studies are in agreement with those of Boothby [36] that the treatment of myasthenia gravis, like the management of diabetes, must be adapted to the individual patient.

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34. Koppanyi, T.; Linegar, C. R., and Dille, J. M.: New Pharmacological Actions of Physostigmine, Proc. Soc. Exper. Biol. & Med. **33**:438, 1935.

35. Crittenden, P. J.: Effects of Anesthetics on the Response of Submaxillary and Pancreatic Glands to Prostigmine and Physostigmine, Proc. Soc. Exper. Biol. & Med. **41**:367, 1939.

36. Boothby, W. M.: Personal communication to the authors. Dr. Boothby has made this statement on many occasions in his discussions at medical meetings, but apparently has not written it in any of his articles.

COMPARISON OF EFFECTS OF PROSTIGMINE AND PHYSOSTIGMINE

The effects of prostigmine and those of physostigmine on voluntary muscle and other structures were compared in 2 patients with myasthenia gravis. These observations were repeated several times on each subject. In order to have a basis for quantitative comparison, the dosage was so regulated that the inhibitory effects of the drugs on the serum esterase activity were similar in comparable experiments.

An attempt was made to obtain a quantitative estimate of the muscular effects in the following manner: During the experiments on the comparison of the drugs, prostigmine methylsulfate and physostigmine salicylate were given on alternate days. For about one hour before the administration of the drug and for three hours thereafter the function of the extraocular muscles and of the muscles of the extremities, face and eyelids was examined at five or ten minute intervals. Fatigability was determined by having the various groups of muscles perform certain test activities. The activity of the serum choline esterase was estimated at frequent intervals, including the period (*a*) before the drug was given; (*b*) when the effects of the drug first were apparent; (*c*) when the effects were maximal, and (*d*) when the effects were diminishing. The subjects had been studied for periods of a few months, and the daily fluctuations in muscular symptoms and the response to prostigmine were well understood.

The data presented in figure 3 are typical of the observations in all these experiments. In brief, the results were as follows: When prostigmine methylsulfate was given the effects on voluntary muscle, as shown by improvement in muscular function, appeared earlier, were of greater magnitude and persisted longer than when physostigmine salicylate was given; prostigmine had less effect on other organs than had physostigmine. With the doses employed, prostigmine had satisfactory therapeutic effect on the muscles without appreciable side effects. On the other hand, the administration of physostigmine was followed by considerable dizziness, diaphoresis, abdominal cramps, nausea and vomiting. When physostigmine was administered, atropine usually was required for relief from these undesirable side effects, whereas when prostigmine was given atropine was needed only when large doses had been administered. Physostigmine had much less effect on voluntary muscles than had prostigmine, even when all undesirable side effects were prevented by the previous administration of adequate amounts of atropine. These results are not in agreement with the conclusions of Briscoe,[12] who studied the effects of both drugs on isolated muscle and concluded there was no reason to suppose that prostigmine had any particular advantage over physostigmine. The difference in the magnitude of effect on the muscular symptoms when prostigmine and when physostigmine was administered is of pharmacologic interest. If the effect on the muscles

is due entirely to the depression of the choline esterase activity, then the two drugs should have produced equal effects in comparable experiments in which the changes in esterase activity were similar. The results suggest that the therapeutic effects of prostigmine and of physostigmine in cases of myasthenia gravis are due largely, but not entirely, to the depression in the activity of the choline esterase and that part of the effect probably is due to direct action on the muscle itself. This interpretation appears to be inescapable, on the basis of the data furnished

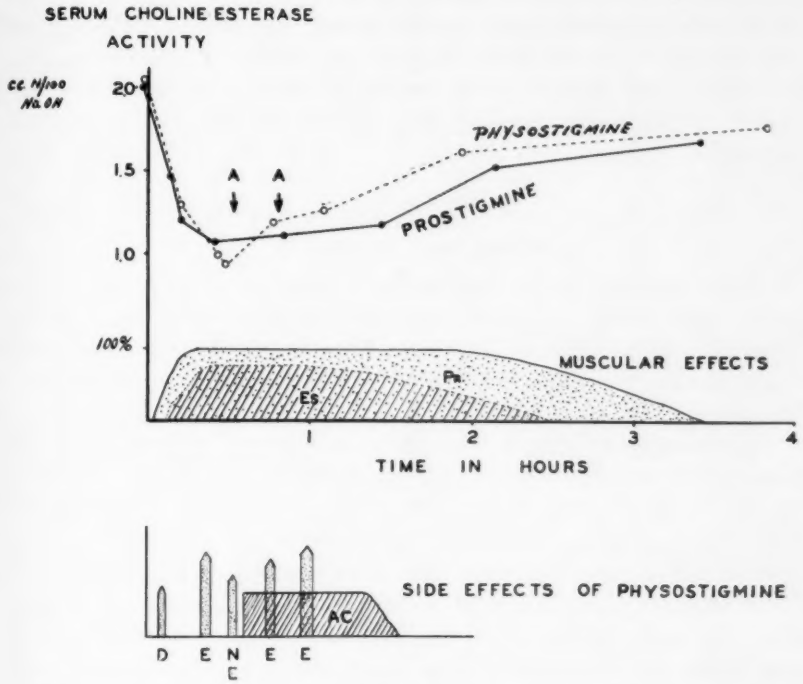

Fig. 3.—Comparison of effects of prostigmine and physostigmine in a patient with myasthenia gravis (case 10). Injection of 1.3 mg. of physostigmine salicylate induced about the same changes in the serum choline esterase activity as did injection of 1.75 mg. of prostigmine methylsulfate. The improvement in muscular function following injection of prostigmine (*Pr*) appeared earlier, was of greater magnitude and persisted longer than that following physostigmine (*Es*). Prostigmine induced no side effects in this experiment, whereas physostigmine caused dizziness (*D*), nausea (*N*), vomiting (*E*) and abdominal cramps (*AC*), which required 0.6 mg. of atropine sulfate twice (*A*).

by these investigations, and is supported by the observations of Rosenblueth and Luco [37] on denervated cat muscle. These authors stated the

37. Rosenblueth, A., and Luco, J. V.: A Study of Denervated Mammalian Skeletal Muscle, Am. J. Physiol. **120**:781, 1937.

opinion that the reduction of the threshold to acetylcholine observed after the administration of prostigmine and physostigmine was due to the antiesterase action of these drugs, whereas the effect of physostigmine on the spontaneous electrical activity and the depressing effects of physostigmine and prostigmine on the electrical excitability of the muscle were the result of some direct action on the muscle.

The observations of Kahlson and Uvnäs [38] also are in agreement with the formulation given in the present report. These workers studied the relation between the sensitivity of the muscle of the frog to acetylcholine and the changes in esterase activity induced by physostigmine and fluoride. They concluded that the inactivation of the esterase could not explain the increase in the sensitivity to acetylcholine and that a change in the receptors which are sensitive to acetylcholine must be postulated.

EFFECT OF ACTIVITY ON MUSCULAR SYMPTOMS AND ON REQUIREMENT OF PROSTIGMINE

That muscular activity will increase weakness in myasthenia gravis is too well known to warrant much discussion in this report. Indeed, fatigability of the muscles constitutes the outstanding complaint in this condition, and the therapeutic value of rest has been recognized for a long time.

In the present studies, the effect of muscular exercise has been investigated with reference to changes in the choline esterase activity of the serum and to the requirements for prostigmine. The muscular fatigue and weakness induced by activity were not associated with any spontaneous change in the esterase activity of the serum in any of the 10 patients in whom this relation was studied. However, all patients who were more than only slightly ill required larger amounts of prostigmine when they were active than when activity was restricted. In all these instances the esterase activity of the serum had to be depressed to lower levels during periods of increased activity.

A striking demonstration of the effects of complete rest and of muscular activity on the symptoms of a seriously ill patient (case 2) is illustrated in figure 4. In brief, the observations were as follows: The patient was confined to bed. She lay comparatively quiet, but her movements were not restricted. Relatively large doses of prostigmine were required. On several successive days, the muscular disability showed a definite relation to the level of serum esterase activity. The patient required prostigmine at frequent intervals during the day and,

38. Kahlson, G., and Uvnäs, B.: Zur Theorie der Sensibilisierung für Azetylcholine, zugleich Bericht über eine erregbarkeitssteigernde Wirkung des Fluorids, Skandinav. Arch. f. Physiol. **72**:215, 1935.

in addition, was given the drug during the night. When the esterase level was around 1.25 the amount of disability was estimated to be about 50 per cent, and when the esterase level was depressed to about 1.0 the disability decreased to an amount estimated to be in the neighborhood of 30 per cent. On the third evening following these observations the patient was informed that no medication would be given during the night, but that the physician would continually be available at the bedside with a syringe containing prostigmine methylsulfate ready for immediate administration. The patient was asked that on awakening she make no muscular movement other than merely to raise the eyelids to indicate that she was awake. She was most cooperative. She slept well and was unusually quiet during the entire night. On awakening she was

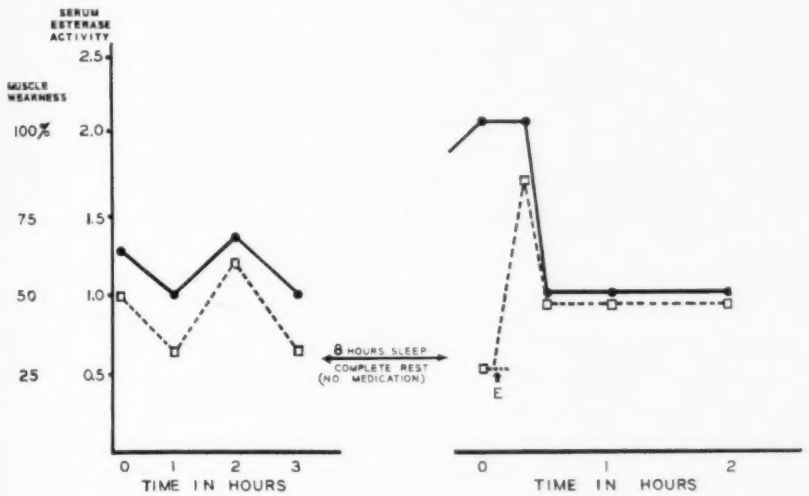

Fig. 4.—The effect of physical activity on muscular weakness and on the requirement of prostigmine (case 2). The solid line represents the level of serum esterase activity, and the broken line, the amount of muscular weakness. The changes occurring during a typical day, with moderate limitation of physical activity, are shown on the left side of the chart. Note the low levels to which the esterase activity had to be depressed by administration of prostigmine in order to maintain respiratory function. The right side of the chart shows the effect of avoidance of all physical activity. The function of respiratory muscles was normal despite the high esterase level until the patient exercised slightly, indicated at *E*. This slight exertion precipitated an immediate and alarming exacerbation of muscular weakness. Administration of prostigmine lowered the esterase activity and restored muscular function.

reminded to remain perfectly still. She appeared to be comfortable; the respiratory movements were normal, and the facial and extraocular muscles showed only slight weakness on cautious examination. The serum esterase activity was 2.2, an astonishingly high level for her at this

time in the course of her illness. On the preceding days the patient had been excessively weak whenever the serum esterase activity had been permitted to rise to 1.5; yet during the period of sleep and almost complete muscular rest the esterase level had gradually risen to the high level of 2.2 without involvement of the respiratory muscles.

As soon as these observations had been made, the patient was asked to raise the arms over the head a few times. This slight activity was followed almost immediately by sudden weakness of most of the muscles. Within two minutes severe respiratory difficulty developed. The face was immobile; there was definite limitation of extraocular movements, and the patient was unable to talk. Muscular weakness involved practically all the muscles and was extreme. Later in the day, after her condition had improved after medication, she stated that her throat had felt "as tight as a vise."

Prostigmine methylsulfate was administered almost immediately. In about three minutes muscular function improved, and in another seven minutes muscular weakness was only moderate. During the rest of the day and the next few days the relation between the level of esterase activity and the amount of muscular disability was of the same order as that observed on the days of control previously discussed.

EFFECT OF ACUTE INFECTION (PHARYNGITIS DUE TO BETA HEMOLYTIC STREPTOCOCCUS) ON THE MUSCULAR SYMPTOMS AND ON THE THERAPEUTIC EFFECTS OF PROSTIGMINE

The opportunity of studying these phenomena was presented when a beta hemolytic streptococcic infection of the pharynx developed in a patient (case 6) during the period of investigation. During the two weeks prior to the infection the patient required oral administration of 15 mg. of prostigmine bromide three times a day. Attacks of respiratory difficulty, which the patient had when she was admitted to the hospital and for which the subcutaneous administration of 0.5 mg. of prostigmine methylsulfate had been necessary, no longer occurred after the patient had rested in bed for a few days.

With the onset of the acute infection of the pharynx the muscular disability increased rapidly, and attacks of respiratory distress occurred with increasing frequency. The amount of prostigmine methylsulfate had to be increased so that the patient was given as much as 6.5 mg. subcutaneously (in ten injections) on one day, in addition to the basal dose of 15 mg. of prostigmine bromide three times daily by mouth. During the period preceding the infection, muscular weakness was pronounced when the activity of the serum choline esterase was about 2.2 and small amounts of prostigmine were effective in relieving the symp-

toms. Only slight inhibition of the serum esterase activity, to a level of about 2.0, was accompanied by definite improvement in symptoms.

In contrast to these observations were those made during the period of infection. Large amounts of prostigmine methylsulfate were necessary, and the esterase activity had to be depressed to much lower levels. When the activity of the choline esterase was permitted to rise to a level of about 1.65, severe muscular weakness and extreme respiratory distress occurred, and further inhibition of the esterase activity to a level as low as 1.15 was required for significant improvement in the symptoms. Muscular activity, such as that entailed by coughing, induced exacerbation of symptoms even when the esterase level was low. Moreover, the muscular activity increased the requirements of prostigmine, and at such times improvement was induced only when the esterase was inhibited to a greater extent than that required after periods of rest. The effect of the infection and that of muscular activity on the muscular symptoms and on the requirements of prostigmine appeared to be additive.

As the acute infection subsided the muscular symptoms gradually returned to their previous status. At the time the patient left the hospital the serum esterase levels during periods of muscular weakness were the same as those during similar periods previous to the onset of infection. Moreover, improvement in muscular symptoms required only about the same inhibition of esterase activity as that before the infection.

EFFECT OF THE MENSTRUAL CYCLE ON MUSCULAR SYMPTOMS, SERUM ESTERASE ACTIVITY AND REQUIREMENTS OF PROSTIGMINE

Nine of the female patients in this series gave a history of exacerbation of muscular weakness and fatigability during the menstrual period. Usually the increase in symptoms was most pronounced during the first day or two of the period. Most of these patients found it necessary to restrict their activities on these days, even when increased amounts of prostigmine were taken. Moreover, amounts of prostigmine that had a satisfactory effect on muscular symptoms on the days between the menstrual periods often gave only slight and delayed effects during the first few days of menstruation.

These changes in muscular symptoms were not accompanied by any significant alterations in the resting esterase level of the serum. However, during the menstrual period a greater degree of inhibition of the choline esterase activity often was required for improvement of symptoms than on the days between the menstrual periods. Therefore increased amounts of prostigmine were needed for clinical improvement.

On the other hand, 1 patient (case 3) usually felt improved during the entire menstrual period and was able to reduce the dose of prostigmine at this time.

The effect of menstruation on muscular disability is a common observation, but is not uniform. It is likely that the relation is not of etiologic importance and is merely of the same order as that observed in many clinical conditions in which the severity of symptoms is increased during menstruation. The effect of estradiol benzoate (progynon B) in 1 patient was to increase the disability, whereas the administration of testosterone propionate was followed by slight improvement. This patient had had a remission during pregnancy; after the termination of the pregnancy by abortion the symptoms returned. In another patient (case 9) the onset of muscular symptoms occurred when she was delivered of a premature baby. Fearnsides,[39] Reuter [40] and Silverstein [41] observed patients whose symptoms were improved during pregnancy, but Laurent's [42] patient, who had complete remission during the first two pregnancies, suffered from serious relapses during five subsequent pregnancies. It would appear that pregnancy often can have a profound influence on the symptoms of myasthenia gravis, but this effect is not uniform and is unpredictable.

DIMINISHING EFFECT OF PROSTIGMINE ON MUSCULAR FUNCTION IN PATIENTS FATALLY ILL WITH MYASTHENIA GRAVIS

The histories of 3 patients (cases 1, 2 and 3) demonstrate that the effect of prostigmine on muscular function can diminish in patients who are seriously ill. One patient (case 1) was observed before the present investigations on choline esterase were started; therefore no information on the esterase activity can be given. However, the observations made in this case showed that progressively increasing doses of the drug were required to maintain respiratory function and that the effect of the drug decreased in amount and duration during the course of the illness. Shortly before the time the patient died prostigmine had practically no beneficial effect on muscular function, whereas earlier in the course of the disease prostigmine had a definite effect on the muscular symptoms.

In another patient (case 3) the effect of prostigmine was the almost complete disappearance of muscular symptoms when the drug was administered during a period in which the patient was only moderately

39. Fearnsides, E. G.: Myasthenia Gravis and Epileptiform Attacks Observed Over a Period of Eleven Years, Proc. Roy. Soc. Med. (Sect. Neurol.) **9**:48, 1915-1916.

40. Reuter, A.: Zur Kenntnis der Myasthenia gravis, Deutsche Ztschr. f. Nervenh. **120**:131, 1931.

41. Silverstein, A., in discussion on Milhorat, A. T.: Chemical and Pharmacologic Studies on Diseases of Muscle, Arch. Neurol. & Psychiat. **41**:1260 (June) 1939.

42. Laurent, L. P. E.: Remissions and Relapses Associated with Pregnancy in Myasthenia Gravis, Lancet **1**:753, 1931.

ill, whereas eleven months later, when the patient was seriously ill, prostigmine was practically without effect (fig. 5).

The third patient (case 2) was studied carefully over the period of three and one-half months in which she was in the special research ward. Esterase studies were made practically every day, and often several observations were made on the same day. The data, presented in figure 6, show that the activity of the choline esterase had to be depressed to progressively lower levels during the course of the patient's stay in the hospital. This required progressively increasing amounts of prostig-

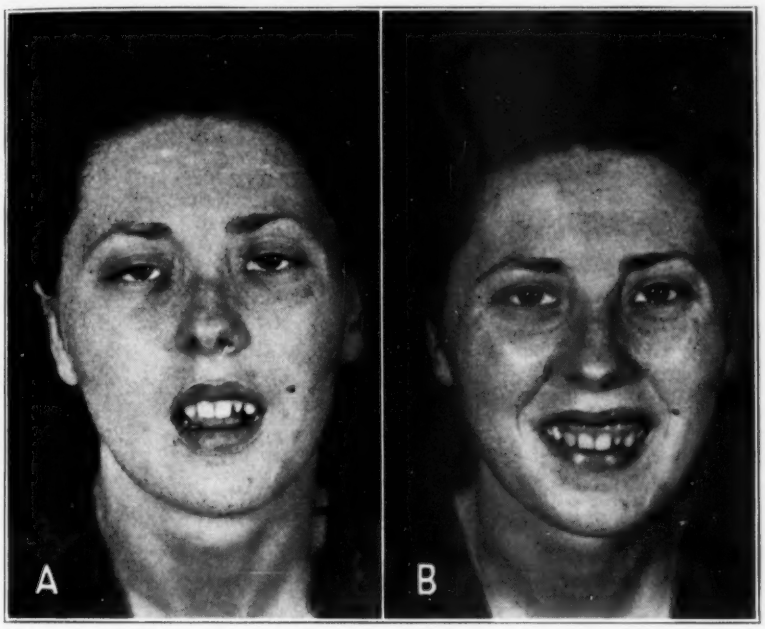

Fig. 5.—Effect of prostigmine on a patient with myasthenia gravis (case 3). *A* shows an attempt to smile before administration of the drug. *B* was taken fifteen minutes after the subcutaneous injection of 1.5 mg. of prostigmine methylsulfate.

Eleven months later, during a period of exacerbation of the patient's symptoms, prostigmine was practically without effect.

mine, the effect of which on the muscles gradually diminished both in amount and in duration. Thus, during the early part of the patient's stay in the hospital a good therapeutic response was obtained with prostigmine whenever the esterase activity was depressed only slightly. Later the esterase activity had to be depressed to much lower levels to produce a satisfactory effect on muscular function. Toward the end of the period of observation, and shortly before the patient died, practically no response

was obtained even when the inhibition of esterase activity was considerable. This phenomenon was limited to the response of the voluntary muscles, which appeared to have become increasingly refractory to stimulation. A diminishing effect of prostigmine on the activity of choline esterase or on structures other than voluntary muscle could not be demonstrated.

All 3 of these patients had to be put in the respirator because of respiratory failure, although prostigmine was given at frequent intervals. An observation which appears not to have been emphasized heretofore

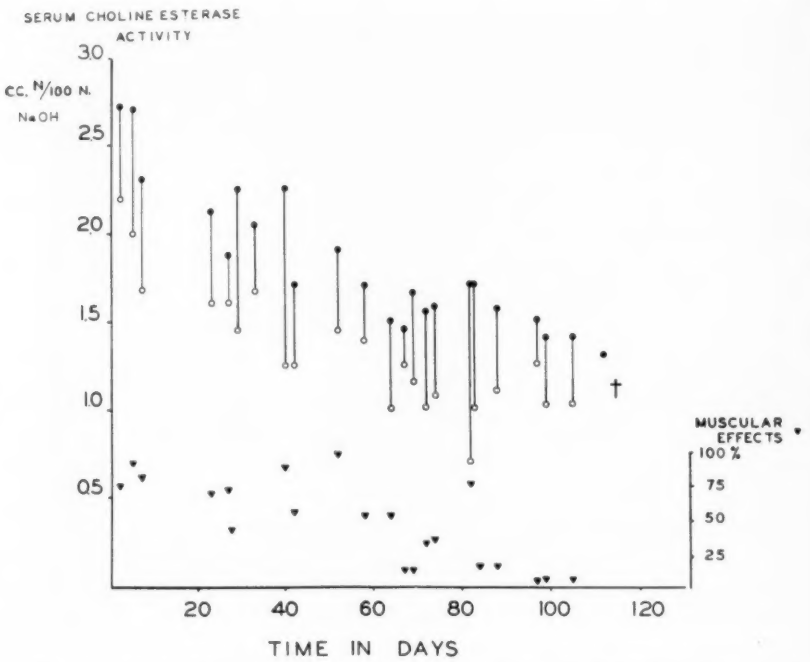

Fig. 6.—Diminishing effect of prostigmine in a patient fatally ill with myasthenia gravis (case 2). Prostigmine bromide (30 mg.) was given orally every four hours. The solid circles indicate the level of serum choline esterase activity when severe muscular weakness developed and additional injection of prostigmine methylsulfate was required immediately. The open circles indicate the level to which the esterase activity was depressed by the additional prostigmine. The solid triangles show the amount of functional improvement induced by this depression in the choline esterase activity. At † no effect of prostigmine was obtained, and the patient died.

is the development of cyanosis while such patients are in the respirator. The 3 patients who were placed in the respirator had several attacks of severe cyanosis, although good respiratory function was maintained by the apparatus. It is puzzling that such episodes should occur under

these circumstances. Many of the attacks could be abolished by the administration of prostigmine, but the effects of the medication gradually diminished until the drug appeared to be entirely ineffective. It is possible that the attacks of cyanosis were due in part to some disturbance in cardiac function. Boothby [43] stated the opinion that there is both pathologic and clinical evidence that occasionally the heart muscle is affected in myasthenia gravis. Whether serious cardiac involvement exists in the late stages of the disease and is of importance in determining the course of the illness cannot be stated with certainty at this time. Unfortunately, the construction of the respirator made adequate studies of cardiac function in these patients impossible. The fact remains that the treatment of patients seriously ill with myasthenia gravis still is unsatisfactory, and this important phase in the management of patients with the disease warrants further investigation.

METABOLISM OF CREATINE IN PATIENTS SERIOUSLY ILL WITH MYASTHENIA GRAVIS

Extensive data on the metabolism of creatine in patients with myasthenia gravis are not presented in this report, as this subject already has been discussed in an earlier article of this series (Milhorat and Wolff [44]). However, certain additional observations on the metabolism of creatine in patients seriously ill with myasthenia gravis are of interest.

Two patients (cases 1 and 2) entered the hospital with severe exacerbations of symptoms. Both patients required increasing amounts of prostigmine, which finally produced only minimal effects on the voluntary muscles. Both patients died. It is interesting that these patients showed evidence of serious involvement of the metabolism of creatine, in that the daily output of urinary creatine was high (0.300 to 0.400 Gm.) and the creatine tolerance was impaired (35 to 70 per cent). One of these patients (case 2) had been observed over a period of several years, but up to the time of her last admission the metabolism of creatine had been normal. During the same period the patient had had several severe exacerbations of symptoms, but each time with rest and medication she improved.

In contrast to the findings in these 2 cases were those in 2 others (cases 6 and 3). Both patients were observed during periods of severe muscular involvement and respiratory distress. Although very ill, they

43. Boothby, W. M.: Myasthenia Gravis: IV. The Onset and Course of the Disease, J. A. M. A. **102**:259 (Jan. 27) 1934; Myasthenia Gravis: V. Effect of Treatment with Glycine and Ephedrine, Proc. Staff Meet., Mayo Clin. **9**:593, 1934.

44. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: III. Metabolism of Creatine and Creatinine in Myasthenia Gravis, Including a Study of the Excretion of Nucleosides and Nucleotides, Arch. Neurol. & Psychiat. **39**:354 (Feb.) 1938.

responded to treatment. The metabolism of creatine in both instances was practically normal (daily urinary creatine, 0.030 Gm.; creatine tolerance, 70 to 81 per cent). However, 1 of these patients (case 3) subsequently had another severe exacerbation of muscular disability and died. She was too ill at this time to permit any studies of the metabolism of creatine.

The findings are in agreement with the formulation made in the previous report that when gross changes in the metabolism of creatine occur in myasthenia gravis and are not due to some accompanying condition, such as hyperthyroidism, the prognosis for life is apt to be grave. On the other hand, the data do not justify the inference that when the metabolism of creatine is normal the prognosis for life is favorable. Patients with myasthenia gravis who are seriously ill often show no significant change in the metabolism of creatine.

EXACERBATION OF MUSCULAR SYMPTOMS INDUCED BY LARGE DOSES OF PROSTIGMINE

The effects of large doses of prostigmine methylsulfate were studied in a series of experiments on 5 patients. The amount of the drug used was from 2 to 2.5 mg., administered subcutaneously. In every instance the immediate effect of the prostigmine was improvement in muscular weakness and fatigability, which was apparent within a minute after the injection of the drug and persisted from two to three hours. However, during the third or fourth hour after the administration of the prostigmine definite exacerbation of muscular disability occurred. This increase in muscular weakness usually occurred at a time when the level of the esterase activity of the serum still was below the level for the period before the injection of the drug. The relation between the changes in the serum esterase and those in muscular disability is shown in figure 7.

In the experiments in which the patients were permitted to engage in muscular activity during the period immediately following the injection of prostigmine methylsulfate the subsequent exacerbation of symptoms was greater than when the patients were required to rest in bed throughout the experiment. Even when muscular rest was complete, however, definite increase in muscular disability was observed during the period when the esterase activity of the serum was returning to its previous level. The administration of additional prostigmine methylsulfate improved the muscular symptoms, but in some instances the effect obtained from this administration was less than on other occasions. It would appear that the exacerbation in muscular weakness following the administration of large doses of prostigmine is due to two factors: first, the increased muscular activity of which the patients are capable during the period of improvement, and, second, a partially refractory state in the muscle induced by the excessive stimulation of the drug.

This effect is quite different from that described by Briscoe,[45] who observed a curare effect when large doses of prostigmine were used. The effect studied by Briscoe occurred during the period when the action of prostigmine was at its height; the effect studied in the present investigations occurred during the period when the action of the drug had almost subsided. Moreover, the effect described here could be abolished by the additional administration of prostigmine. Moore [27] reported an instance of exacerbation which followed the use of large doses of prostigmine and was relieved by administration of additional prostigmine. The increased refractoriness of the muscle after large doses of prostigmine is of importance in the management of ambulatory patients; in the treatment of seriously ill patients whose muscles have become increasingly

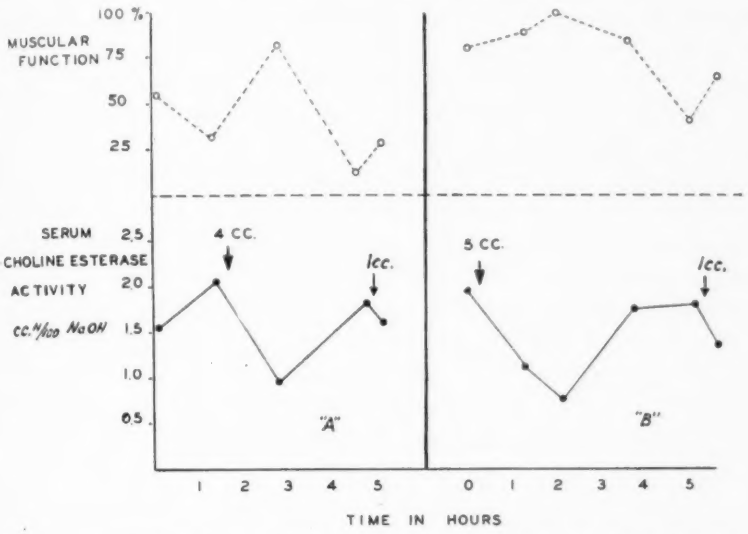

Fig. 7.—Exacerbation of muscular symptoms following the administration of large amounts of prostigmine (cases 10 and 4). The increase in muscular disability occurred at the time that the effects of prostigmine methylsulfate were subsiding and before the activity of the serum esterase had returned to its previous level. Injection of 1 cc. of a 1:2,000 solution lowered the esterase level and induced improvement in muscular symptoms.

refractory to cholinergic nerve stimulation this additional factor might possibly influence the outcome.

SIDE EFFECTS OF PROSTIGMINE

Most of the patients in this series experienced no undesirable side effects of prostigmine when doses sufficiently large to have therapeutic

45. Briscoe, G.: Depressant Peripheral Effect of Prostigmin and Its Temporary Antagonism by Curarine, J. Physiol. **86**:1P, 1935; The Antagonism Between Curarine and Acetylcholine, ibid. **87**:425, 1936.

effects on muscular function were given. However, the administration of unduly large amounts of the drug produced dizziness, a feeling of faintness, sweating, tachycardia, nausea, vomiting and abdominal cramps. Very ill patients who required large amounts of prostigmine often experienced these undesirable side effects of the drug, unless atropine was administered. Atropine sulfate in amounts of from 0.6 to 1.0 mg. prevented and abolished these side effects.

In the present studies, certain other interesting side effects of prostigmine were observed. While their occurrences must be infrequent, these effects are of importance in an understanding of the pharmacologic action and therapeutic use of the drug.

Auricular Fibrillation.—A patient (case 2) who was given large amounts of prostigmine bromide by mouth and, in addition, occasional subcutaneous injections of prostigmine methylsulfate had on two occasions complete asystole of the heart, followed by auricular fibrillation. The amounts of prostigmine given at these times did not differ significantly from those given on most of the other days during a period of several weeks. The cardiac involvement was preceded by sweating, pallor and a feeling of faintness, followed in a few minutes by complete stoppage of the heart for about ten seconds and accompanied by generalized convulsions. When cardiac action returned the rhythm was totally irregular for about two hours. Electrocardiographic changes were typical of auricular fibrillation. In both instances the choline esterase activity of the serum was unusually low; on one occasion it was only 0.18. Although atropine sulfate was administered by subcutaneous injection as soon as the heart had stopped, the return of cardiac function occurred before much of the drug probably had been absorbed. A more detailed report of these observations will be made elsewhere.

The sudden and unusual increase in the action of prostigmine, as indicated by the pronounced side effects and the marked inhibition of the serum esterase activity, possibly was due to increased absorption of prostigmine bromide from the intestinal tract. Considerable variation in the intestinal absorption of prostigmine bromide was not observed in other patients, but Goodman and Bruckner [46] have described an instance in which prostigmine bromide appeared to be absorbed in unusually large amounts. They reported the experiences of a normal subject in whom severe manifestations of prostigmine poisoning developed after the oral administration of 45 mg. of the drug, although doses of 30 mg. had been taken on several occasions previously without appreciable effects.

46. Goodman, L. S., and Bruckner, W. J.: The Therapeutics of Prostigmin: A Warning Concerning Its Oral Use Based on a Personal Experience, J. A. M. A. **108**:965 (March 30) 1937.

Bronchial Asthma.—A patient (case 15) for whom a diagnosis of myasthenia gravis had been made, although subsequent study in these investigations disclosed no evidence of the condition, had severe attacks of bronchial asthma whenever prostigmine methylsulfate was given. After the withdrawal of the drug the asthma promptly subsided entirely (see case history).

EFFECT OF GUANIDINE, PILOCARPINE, ERGOTAMINE TARTRATE AND ACETYLBETAMETHYLCHOLINE

The data on the effects of these drugs are summarized in the table and are compared with those of prostigmine and physostigmine.

Guanidine.—The effect of guanidine was studied in a series of observations on 3 patients. The following data on 1 patient (case 10) are

Effect of Various Substances in Cases of Myasthenia Gravis

Substance	Effect on Muscular Function	Effect on Choline Esterase Activity	Influence on Muscular Effects of Prostigmine	Side Effects †
Prostigmine	++++	++++	..	+
Physostigmine	+++	++++	..	+++
Guanidine	++	0	0	+
Pilocarpine	0	0	0	+++
Ergotamine tartrate	0	0	0	±
Acetylbetamethylcholine	0	0	0	++++
Ephedrine	+ to ++	0	0	±

* This rough comparison is based on data obtained by the administration of the usual therapeutic doses of the substance. No comparison of the effects of similar amounts is made.
† Effects on structures other than voluntary muscle.

typical: Guanidine and prostigmine in varying amounts, were given on alternate days, and the muscular effects of the two substances were compared. Oral administration of 600 mg. of guanidine hydrochloride induced about the same amount of muscular improvement as subcutaneous injection of 0.5 mg. of prostigmine methylsulfate, and the effect of 1.0 Gm. of the guanidine salt was about equivalent to 0.75 mg. of prostigmine methylsulfate. When prostigmine was administered after guanidine and at the time when the effect of the guanidine was established, the effects of the two substances were observed to be additive. For example, the effect of 600 mg. of guanidine hydrochloride followed forty minutes later by subcutaneous injection of 0.5 mg. of prostigmine methylsulfate was about the same as that of 1.0 mg. of prostigmine methylsulfate. There was no evidence that guanidine increased the effects of prostigmine on muscular function. In other words, although Feng [47] observed

47. Feng, T. P.: Studies on the Neuromuscular Junction: X. The Effects of Guanidine, Chinese J. Physiol. **13**:119, 1938.

that guanidine rendered the muscle more responsive to stimulation, the observations on these patients do not indicate that the drug increases the therapeutic effects of prostigmine. Observations on the effects of guanidine in patients whose muscles had become refractory to the action of prostigmine would be of practical and theoretic interest. Amounts of guanidine hydrochloride large enough to give effects greater than those of about 1.0 mg. of prostigmine methylsulfate (2 cc. of a 1:2,000 solution, given subcutaneously) usually produced subjective side effects, such as a tingling sensation in the tongue.

Guanidine was observed to be without effect on the choline esterase of the serum. For example, the resting value of the serum esterase of 1 patient (case 10) was 2.20. Guanidine hydrochloride (600 mg.) was given by mouth, and forty-four minutes later the improvement in muscular function was about equivalent to that induced by 0.5 mg. of prostigmine methylsulfate, given subcutaneously. However, the serum esterase activity was unchanged, namely, 2.20, whereas 0.5 mg. of prostigmine methylsulfate (1 cc. of a 1:2,000 solution) lowered the esterase activity to 1.60.

Minot, Dodd and Riven [48] observed that guanidine hydrochloride was useful in the treatment of patients with myasthenia gravis. The observations on guanidine which were made during the present investigations were not as extensive as those of Minot and her co-workers. It is possible that further studies will establish the usefulness of this substance in the management of patients with myasthenia gravis, but the present findings suggest that guanidine has no advantage over prostigmine when used alone or in conjunction with prostigmine.

Pilocarpine.—Pilocarpine hydrochloride given subcutaneously in amounts of 0.4 to 0.6 mg. had no effect on muscular function or on the esterase activity of the serum. The profuse sweating induced by the drug was abolished promptly by atropine.

Ergotamine Tartrate.—The effect of ergotamine tartrate was studied in 2 patients (cases 4 and 8). The subcutaneous administration of 0.3 cc. of a 1:2,000 solution was without effect on the muscular symptoms. Moreover, the subsequent administration of prostigmine had effects that were similar to those seen in these patients when no ergotamine had been given previously. Ergotamine had no effect on the serum esterase activity either in the patients or when added to serum in a test tube.

Acetylbetamethylcholine.—Two patients were given acetylbetamethylcholine hydrochloride orally in doses up to 300 mg. No effect on

48. Minot, A. S.; Dodd, K., and Riven, S. S.: The Response of the Myasthenic State to Guanidine Hydrochloride, Science **87**:348, 1938; Use of Guanidine Hydrochloride in the Treatment of Myasthenia Gravis, J. A. M. A. **113**:553 (Aug. 12) 1939.

the muscular symptoms was observed. Prostigmine bromide given together with acetylbetamethylcholine hydrochloride had about the same effect on the voluntary muscles as had prostigmine alone. These observations on acetylbetamethylcholine are at variance with those of Fraser, McGeorge and Murphy,[49] who reported that the administration of acetylcholine chloride and acetylbetamethylcholine hydrochloride was followed by improvement in muscular function for periods as long as several hours. The prolonged effect reported by these authors is surprising. It is difficult to understand how the muscular effects can persist for so long a period, since the substances are rapidly inactivated in the body.

PROSTIGMINE AS AN AID IN THE DIAGNOSIS OF MYASTHENIA GRAVIS

Prostigmine was administered to a large number of patients with muscular disorders other than myasthenia gravis. However, inasmuch as this phase of the study already has been investigated by other workers, no details of the data are presented.

Viets and Schwab,[50] Viets and Mitchell,[51] Gammon and Scheie [52] and Harvey and Whitehill [23] suggested the use of prostigmine as a diagnostic aid. These workers observed that the administration of prostigmine induced improvement in muscular symptoms only in patients with myasthenia gravis; the drug was without effect in patients with other conditions. On the other hand, Hamill and Walker [53] found prostigmine to have a beneficial effect in a variety of conditions, including amyotrophic lateral sclerosis, and Winkelman and Moore [22] found some increase in muscular power when the drug was administered to patients in the early stages of progressive muscular dystrophy. The observations made in the present investigation are in agreement with those of Viets and Schwab and the other workers who found prostigmine to be effective only in patients with myasthenia gravis. Since the manifestations of myasthenia gravis can be bizarre and the diagnosis in the early stages a matter of some difficulty, the use of prostigmine as a diagnostic aid is of considerable aid.

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49. Fraser, F. R.; McGeorge, M., and Murphy, G. E.: The Action of Choline Esters in Myasthenia Gravis, Clin. Sc. **3**:77, 1937.

50. Viets, H. R., and Schwab, R. S.: Prostigmin in the Diagnosis of Myasthenia Gravis, New England J. Med. **213**:1280, 1935.

51. Viets, H. R., and Mitchell, R. S.: The Prostigmin Test in Myasthenia Gravis: Second Report, New England J. Med. **215**:1064, 1936.

52. Gammon, G. D., and Scheie, H.: Use of Prostigmin as a Diagnostic Test of Myasthenia Gravis, J. A. M. A. **109**:413 (Aug. 7) 1937.

53. Hamill, P., and Walker, M. B.: The Action of "Prostigmin" (Roche) in Neuro-Muscular Disorders, J. Physiol. **84**:36P, 1935.

This observation was of assistance in the management of 3 patients (cases 11, 12 and 13) in whom psychogenic factors were predominant. Evaluation of the history and clinical findings in each case suggested that both myasthenia gravis and psychogenic factors were present. The administration of prostigmine methylsulfate to these patients was followed by definite, but incomplete, improvement in muscular function. All objective evidence of myasthenia gravis could be removed by prostigmine, but the patients still complained of muscular weakness. However, despite protests of feeling tired, the patients could be induced by constant urging to raise the arms repeatedly over the head. In contrast, no amount of urging by the examiner could induce these patients to continue after moderate muscular exercise when prostigmine was not given.

Kennedy and Wolf [54] noted exacerbation of muscular symptoms when quinine was given to patients with myasthenia gravis. These authors and Harvey [10] suggested that the effect of quinine in patients with myasthenia gravis indicates the nature of the defect in this condition. In a recent discussion, Milhorat [55] suggested that the effect of the drug is due merely to an antagonistic action on the stimulation of cholinergic nerves. However, it is probable that quinine can be of use in certain instances in making a diagnosis of myasthenia gravis. It is obvious that the drug must be used with caution, as severe exacerbations might be induced in certain patients.

Another diagnostic aid in certain cases is the study of the metabolism of creatine, namely, the excretion of creatine and the creatine tolerance. Since the metabolism of creatine usually shows no serious defect in cases of myasthenia gravis, the findings are not of assistance in establishing a diagnosis of myasthenia gravis, but they can be of importance in the diagnosis of an accompanying condition of hyperthyroidism. Myasthenia gravis and hyperthyroidism may occur in the same patient, and the difficulty in making the diagnosis can be considerable. Cohen and King [56] published the case of a patient with both conditions and reviewed the reports of 23 similar cases in the literature. Patients with hyperthyroidism often complain of muscular weakness, and when this condition is associated with myasthenia gravis the muscular disability can be profound—hence the importance of recognizing the presence of hyperthyroidism in patients with myasthenia gravis. Creatinuria of considerable magnitude is a common finding in cases of hyperthyroidism

54. Kennedy, F., and Wolf, A.: Quinine in Myotonia and Prostigmin in Myasthenia: A Clinical Evaluation, J. A. M. A. **110**:198 (Jan. 15) 1938; footnote 8.

55. Milhorat, A. T.: Studies in Diseases of Muscle: IX. Effect of Quinine and Prostigmine on Muscular Rigidity in Paralysis Agitans, Arch. Neurol. & Psychiat. **45**:74 (Jan.) 1941.

56. Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**:1338 (Dec.) 1932.

even when the basal metabolic rate is not elevated (Shaffer,[57] Palmer, Carson and Sloan [58] and Shorr, Richardson and Wolff [59]), whereas in myasthenia gravis few changes in the metabolism of creatine occur, except in the late stages of the disease (Adams, Power and Boothby [60] and Milhorat and Wolff [44]). Therefore, in cases of myasthenia gravis in which the patient excretes considerable amounts of creatine and has an impaired creatine tolerance, associated hyperthyroidism should be considered unless the patient either has a rapidly fatal form of the disease or is in an advanced stage of a chronic form of the condition. The use of iodine in such instances is of value in establishing or ruling out the diagnosis of hyperthyroidism, since myasthenia gravis and hyperthyroidism differ significantly in the response to the administration of iodine. The administration of iodine to patients with hyperthyroidism is followed by marked diminution of the creatinuria, as was shown by Palmer, Carson and Sloan [58] and Shorr, Richardson and Wolff,[59] whereas in cases of myasthenia gravis the creatinuria is not affected (Milhorat and Wolff [44]). The administration of thyroid to patients with myasthenia gravis can induce severe exacerbations, as was demonstrated by 1 in this series (case 8). Hines and Knowlton [61] showed that denervated muscle is more easily depleted of its glycogen stores by the administration of thyroid than is normal muscle. The muscles in cases of myasthenia gravis appear to show a similar susceptibility to thyroid administration, although the chemical changes produced in the muscles have not been demonstrated. However, there is much evidence to suggest that in cases of myasthenia gravis the administration of thyroid lowers the glycogen content of the muscle. The evidence includes, first, the exacerbation of symptoms and considerable increase in urinary creatine in cases of various types of muscular wasting when hyperthyroidism develops or when thyroid substance is administered, and, second, the observations of Brentano [62] and of Milhorat, Bartels and

57. Shaffer, P. A.: Protein Metabolism in Exophthalmic Goitre, J. Biol. Chem. **3**:xiii, 1907.

58. Palmer, W. W.; Carson, D. A., and Sloan, L. W.: The Influence of Iodine on the Excretion of Creatine in Exophthalmic Goiter, J. Clin. Investigation **6**:597, 1929.

59. Shorr, E.; Richardson, H. B., and Wolff, H. G.: The Nature of the Muscular Weakness in Graves' Disease, J. Clin. Investigation **12**:966, 1933.

60. Adams, M.; Power, M. H., and Boothby, W. M.: Chemical Studies in Myasthenia Gravis, Ann. Int. Med. **9**:823, 1936.

61. Hines, H. M., and Knowlton, G. C.: The Role of the Nervous System in the Regulation of the Glycogen Metabolism of Skeletal Muscle, Am. J. Physiol. **111**:243, 1935.

62. Brentano, C.: Untersuchungen über die Entstehung der Kreatinurie: II. Die Beziehungen zwischen Kreatinurie und Muskelglykogen, Arch. f. exper. Path. u. Pharmakol. **155**:21, 1930.

Toscani [63] and Milhorat, Hardy, Bartels and Toscani [64] on the relation between certain types of creatinuria and the metabolism of glycogen.

Reuter and Zimmermann [65] studied the metabolism of lactic acid in the blood of patients with myasthenia gravis after muscular exercise and after administration of lactic acid. On the basis of their observations these workers expressed the opinion that the glycogen content of muscle in myasthenia gravis apparently is decreased.

SUMMARY

The choline esterase activity of the blood serum of patients with myasthenia gravis was found to be not unusual and was of the same order as that seen in the large series of patients without this condition.

Spontaneous changes in muscular disability in myasthenia gravis were not accompanied by changes in the esterase activity.

Both prostigmine and physostigmine depressed the activity of the choline esterase. In patients with myasthenia gravis this decrease in the esterase activity usually was accompanied by definite improvement in muscular function, whereas in patients with muscular disability resulting from conditions other than myasthenia gravis no therapeutic effect was observed.

Prostigmine was found to have more effect on striated muscle and less effect on other structures than physostigmine, even when the drugs were given in amounts that had similar effects on the serum esterase activity. The frequent occurrence of undesirable side effects following the administration of physostigmine renders this drug much less useful than prostigmine in the management of patients with myasthenia gravis.

Patients seriously ill with myasthenia gravis often require increasing amounts of prostigmine and the esterase activity has to be kept at progressively lower levels. It appears that the muscles of patients fatally ill with myasthenia gravis become increasingly refractory and require increasing stimulation for contraction. The refractoriness in certain instances can be of such a degree that the therapeutic effects of prostigmine are slight and of short duration.

Patients to whom prostigmine had to be administered at frequent intervals required adequate amounts of atropine for the prevention of undesirable side effects of the prostigmine.

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63. Milhorat, A. T.; Bartels, W. E., and Toscani, V.: Effect of Hepatic Injury on Vitamin C Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:394, 1940.

64. Milhorat, A. T.; Hardy, J. D.; Bartels, W. E., and Toscani, V.: Effect of Shivering, Iodoacetate, and Epinephrine on Vitamin C and Creatine Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:397, 1940.

65. Reuter, A., and Zimmermann, W.: Stoffwechseluntersuchungen bei Myasthenie, Ztschr. f. klin. Med. **124**:99, 1933.

When large amounts of prostigmine were administered an exacerbation of muscular weakness often occurred at the time when the effects of the drug were subsiding and the esterase activity was returning to its previous level. This increase in muscular disability was greater when the patient had been permitted to engage in physical activity. In ambulatory patients maximal benefit was obtained when the smallest amounts of prostigmine that gave satisfactory effects were used.

Numerous factors can increase the muscular symptoms in myasthenia gravis. These include menstruation, infections of the respiratory tract, excessive physical activity and drugs that depress the nervous system. All these factors can increase the requirements of prostigmine, although the effect of the drug on the choline esterase activity is unchanged. The value of limitation of physical activity again is emphasized.

Accompanying hyperthyroidism can seriously alter the course of the disease and induce gross defects in the metabolism of creatine. The changes in the metabolism of creatine following the administration of iodine sometimes are of importance in the diagnosis of an accompanying hyperthyroid condition.

The importance of emotional factors was emphasized in several instances. The use of prostigmine as a diagnostic aid was found to be of value in separating the components in the muscular disability that were the result of myasthenia gravis from those occurring as a psychosomatic reaction in certain of these patients.

Observations on the use of other possible therapeutic agents, including guanidine, pilocarpine, ergotamine tartrate and acetylbetamethylcholine, have been discussed.

Prostigmine is of considerable value in the treatment of myasthenia gravis, but the proper management of patients with this condition includes the recognition and treatment of all factors that might affect the muscular symptoms.

REPORT OF CASES

Myasthenia Gravis.—Case 1.—A housewife aged 40 had a rapidly fatal form of myasthenia gravis. The effect of prostigmine steadily diminished, and the patient had to be placed in the respirator. The case was reported by Milhorat and Wolff [44] (case 7 of that series).

Case 2.—A married woman aged 34, a telephone operator, was admitted for the third time to the New York Hospital on March 18, 1937. Three years previously she noticed muscular weakness, at first only of the right hand but one month later of all extremities. At about the same time she began to have double vision whenever the eyes were used a good deal. The menstrual periods were associated always with an increase in the muscular symptoms. The patient was seen at frequent intervals for the next two and a half years and on two occasions was admitted to the New York Hospital. Under a regimen of aminoacetic acid, ephedrine and restricted activity, the course was fairly satisfactory until about five months before the last admission. Four months before entering the

hospital for the third time the patient began to take 7.5 mg. of prostigmine bromide by mouth three times a day, with some improvement in symptoms. Two months later this dose was increased to 15 mg. three times a day. The muscular weakness increased steadily, so that on awakening in the morning the patient was unable to lift her head from the pillow unless prostigmine was taken. Diplopia became more frequent and occurred several times a day. The patient had frequent difficulty in swallowing, and as a result lost weight steadily. Two weeks before she was readmitted to the New York Hospital the prostigmine bromide was increased to 15 mg. given by mouth every four hours. For the two weeks preceding her admission the patient had considerable difficulty in swallowing and was able to take only small amounts of food and liquids.

Examination showed evidence of dehydration and recent loss of weight. The face was immobile, the forehead could not be wrinkled and the face could not be drawn into a smile or grimace. The voice was weak and husky. The tongue could be protruded only about ½ inch (1.27 cm.). There were ptosis of the left lid and inability to close the eyes tightly. The eyes could be moved without difficulty toward the right, but there was definite limitation in movement toward the left side. Attempts to move the eyes upward were unsuccessful. The muscles of the neck were weak, so that the head could not be lifted from the pillow. The arms could not be raised from the bed. After the subcutaneous administration of 0.5 mg. of prostigmine methylsulfate the muscular disability largely disappeared. The patient weighed 34 Kg.

Course in the Hospital.—The patient was given oral doses of 15 mg. of prostigmine bromide every four hours. However, attacks of severe respiratory difficulty occurred often, so that it was necessary, a week later, to increase the dose of prostigmine bromide to 30 mg. every four hours. Under this regimen the patient's course was fairly satisfactory for a short time, but she soon required additional medication for relief from the respiratory difficulty. During these episodes the patient had extreme weakness of most of the voluntary muscles, the voice became inaudible, thick stringy mucus accumulated in the mouth and the respiratory movements were difficult and labored. To prevent complete cessation of respiration prostigmine methylsulfate had to be given subcutaneously. However, despite all the measures that were employed, including complete rest in bed and constant expert nursing care, the muscular weakness and fatigability grew progressively worse. The attacks of respiratory distress increased in frequency and severity. As a result, the number of injections of prostigmine methylsulfate had to be increased steadily. Whenever attempts were made to increase the length of time between the injections, the patient had an attack of severe respiratory distress; in a few instances the respiration ceased completely. These episodes required immediate administration of prostigmine. During the brief period which elapsed before the effects of the drug were observed and the patient could again breathe without undue difficulty, artificial respiration was given. The patient stolidly refused to enter the respirator, although the respiratory difficulty increased, and prostigmine had to be given more often. By July 5 an average of 3 mg. of prostigmine methylsulfate (four doses each of 1.5 cc. of a 1:2,000 solution) was given subcutaneously, in addition to the 30 mg. of the bromide given by mouth every four hours. An average of two doses each of 0.6 mg. of atropine sulfate was required daily to prevent the side effects of the prostigmine. The course was progressively downhill. Attacks of extreme muscular weakness and of respiratory failure increased in severity and frequency. Prostigmine had to be given more often. The therapeutic effects of the drug came on more slowly, were less evident and were of decreasing duration. On July 16 a total of 7.5 mg.

of prostigmine methylsulfate (15 cc. of a 1:2,000 solution) had to be given, in eleven injections. The therapeutic effects of the drug were now so slight that the patient was put in the respirator. Despite this measure, attacks of cyanosis continued to occur, and she frequently lapsed into semicoma. Prostigmine was now without apparent effect on any of the symptoms. The pulse steadily became weaker until it was imperceptible. On July 17, the one hundred and twenty-eighth day after her admission to the hospital, she died.

Case 3.—An unmarried woman aged 26 was first seen in the New York Hospital on Jan. 18, 1939, complaining of muscular weakness and attacks of respiratory distress. She had been in good health until two and a half years previously, when she first noticed that the muscles of the legs were weak and fatigued easily on exertion. Both the weakness and the fatigability increased slowly, and six months later the muscles of the neck and arms became involved. At about the same time the patient began to have occasional attacks of diplopia, which persisted.

Aside from daily fluctuations, the muscular disability continued practically unchanged until April 1938, when she started to take 15 mg. of prostigmine bromide orally four times daily. She noticed definite improvement in her disability after taking prostigmine, and thereafter never interrupted the daily administration. The improvement continued for seven months, but about two months before the time she was seen at the hospital the muscular disability increased. She began to have diplopia practically every day and attacks of respiratory difficulty and inability to swallow solid foods every few days. The amount of prostigmine bromide taken by mouth was increased gradually to 15 mg. seven times a day. After the dose of prostigmine had been increased the attacks of respiratory difficulty occurred only occasionally. Ephedrine sulfate, in amounts of about 10 mg., was effectvie in relieving the respiratory distress. Unless the patient took prostigmine she was unable to walk or lift the arms to the level of the shoulders. The accumulation of thick mucus in the throat almost every morning was a bothersome symptom. During the menstrual periods the muscular symptoms often were improved, and less prostigmine was required at this time.

Examination showed definite weakness and fatigability of most of the voluntary muscles. The patient walked with difficulty and supported the chin with the right hand. Attempts to wrinkle the forehead revealed weakness of the muscles. The left external rectus muscle was weak, and the face was flat and expressionless. The tongue could be protruded only about 1 inch (2.54 cm.). The voice was weak and thick, and after a few minutes of talking it became inaudible. The arms could be raised to the level of the shoulders, but after a few attempts they could barely be lifted from the sides of the body. The tendon reflexes were normal. The patient weighed 55 Kg.

Despite continued administration of prostigmine and limitation of activity, the course of the illness was unsatisfactory. Muscular weakness and fatigability increased; the patient often had difficulty in masticating and swallowing food and lost about 10 Kg. of weight. On Nov. 14, 1939 she was admitted to the research metabolism ward. Examination showed considerable weakness and easy fatigability of the muscles of the face and extremities. There were bilateral ptosis and strabismus. The extraocular movements were limited.

Under a regimen of complete rest in bed, a diet rich in calories and vitamins and adequate amounts of prostigmine bromide the patient gained weight slowly, so that by the time she was discharged, on Jan. 20, 1940, her weight had increased about 4 Kg. At this time her general condition appeared to be much

improved. After her discharge from the hospital her course was fairly satisfactory, although activity had to be limited definitely. On May 4, 1940 a severe cough, with symptoms of rhinitis, developed. Because of muscular weakness she had considerable difficulty in coughing up sputum, which had become rather profuse. She found it necessary to increase the amounts of prostigmine steadily, so that by the time she was admitted to the hospital, on May 7, she was taking about 30 mg. of the bromide by mouth six times daily and 0.5 mg. of the methylsulfate by subcutaneous injection every hour.

At the time of her admission, the patient looked both chronically and very acutely ill. Respiratory distress was considerable, and the respirations were labored and gasping. There was moderate cyanosis. Over the lower third of the left lung posteriorly there were dulness on percussion, diminished breath and spoken voice sounds and numerous rales. Just above this area there were bronchial breathing and bronchophony, with numerous rales. The temperature was 38.6 C. (101.5 F.), the pulse rate 90 per minute and the respiratory rate 26 per minute.

Course in the Hospital.—Therapy was instituted the moment the patient arrived in the ward. Prostigmine in amounts required to maintain respiration was given. The amounts of the drug needed were 0.5 mg. of prostigmine methylsulfate given subcutaneously about every thirty minutes. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was administered first by hypodermic clysis and later by infusion. Adequate amounts of fluid containing sodium chloride and dextrose were given parenterally. Three hours after the patient was admitted, respirations ceased entirely and it was necessary to put her in a respirator, where she remained until she died, three days later. The administration of sulfapyridine was continued, but the temperature remained in the neighborhood of 39 C. (102.2 F.), and the pulse rate was about 130 per minute.

Despite the use of the respirator, the patient had rather frequent episodes of considerable respiratory difficulty, associated with cyanosis. These attacks usually subsided promptly when 0.5 to 1.0 mg. of prostigmine methylsulfate was injected subcutaneously. On the evening of the second day she became unconscious for about two hours, but later in the evening seemed to rouse, was cheerful and appeared to be as strong as usual. However, early the following morning she suddenly had another attack of cyanosis while she was in the respirator, the pulse could not be felt and, despite the use of prostigmine and various methods of stimulation, she died. During the last day of her life the patient required subcutaneous injections of 0.5 mg. of prostigmine methylsulfate about every hour, with sufficient atropine sulfate to abolish undesirable side effects of the prostigmine.

The observations at autopsy were those of bronchopneumonia and hyperplasia of the thymus, with proliferation of reticulum cells. Examination of practically all the other organs disclosed no significant anatomic changes.

Case 6.—A housewife aged 34 was admitted to the New York Hospital for the first time on April 14, 1935, complaining of diplopia for seven years and weakness of the arms and legs for six and one-half years. Seven years before her admission to the hospital the patient began to have intermittent diplopia, which persisted until the time of her admission. Six months after the onset of double vision she noticed that her legs tired more easily and, a short time later, that the muscles of the arms fatigued easily after exertion. These symptoms varied in degree from time to time; on some days she felt fairly strong, and on others her weakness was considerable.

Two years before her admission to the hospital the patient noticed that her voice had a nasal character; liquids regurgitated through her nose when she tried to swallow, and her face became expressionless. With varying degrees, the symptoms persisted until the time of her admission. During a pregnancy of six weeks (terminated by medication) the symptoms were much improved. The past personal history was irrelevant. Physical examination in April 1935 showed weakness of the extraocular and orbital muscles and a nasal quality of the voice. The peroneal muscles were weak. The tendon reflexes were hyperactive and not readily fatigued.

After her discharge from the hospital the patient did fairly well on a regimen of 20 Gm. of aminoacetic acid daily, 25 mg. of ephedrine sulfate twice a day and limitation of muscular activity. Two months later she noted increasing palpitation and stopped taking the ephedrine. In October 1936 she started to take 15 mg. of prostigmine bromide orally three times a day and noted definite improvement in muscular symptoms. On a few occasions when she increased the oral dose of prostigmine bromide to 30 mg. three times a day she noticed considerable increase in muscular strength, but this period of improvement was followed in a few days by exacerbation of symptoms.

On Dec. 10, 1937 the patient was readmitted to the hospital for one week. Examination revealed the same condition as at the time of the first admission. Prostigmine bromide given by mouth in amounts of 7.5 mg. three times daily had but little effect on either the choline esterase activity of the serum or the patient's symptoms. When the prostigmine was increased to 15 mg. three times a day satisfactory improvement in the symptoms and appreciable effect on the choline esterase activity were obtained. Under this regimen the patient was able to perform her household duties and engage in limited activities. However, about two months before her third admission, on Jan. 16, 1939, she noted increasing weakness and a decreased effect of prostigmine on the muscular symptoms. For the two weeks preceding her admission she had occasional difficulty of respiration.

Examination on her third admission showed definite weakness of the muscles of the face and extremities. There was ptosis of the left lid, but the extraocular movements were normal. The arms could be raised only to about the level of the shoulders, and further attempts were followed rapidly by extreme weakness of the muscles of the arms. The patient was given 15 mg. of prostigmine bromide orally four times a day. Usually the administration of the drug was followed in about thirty minutes by definite improvement in muscular disability. Occasionally, during the afternoons, the effect of prostigmine was only slight.

On several occasions the patient had considerable difficulty in breathing. This difficulty came on suddenly and, unless relieved by the immediate administration of 0.5 mg. of prostigmine methylsulfate (1 cc. of a 1:2,000 solution) subcutaneously, increased rapidly in severity. The muscular symptoms gradually improved, and after a few days of complete rest in bed the patient required less prostigmine, until, except for the basal oral dose of 15 mg. of the bromide three times a day, none was necessary. On Feb. 4, 1939 (the nineteenth day of her stay in the hospital) the patient felt weak and complained of soreness of the throat. The temperature rose to 39.4 C. (102.9 F.). The pharynx soon became red and injected. Culture of material from the throat showed numerous beta hemolytic streptococci. The patient rapidly became so weak that she could barely open her eyes, and the respiration became irregular and labored. She began to require large subcutaneous doses of prostigmine (a total of 6.5 mg. of prostigmine methylsulfate in ten injections was given on February 6). The use of an oxygen tent

was of considerable value in decreasing the respiratory distress. Sulfanilamide was given for about three days apparently with excellent therapeutic effect on the infection. On February 11 the temperature returned to normal and the muscular symptoms rapidly improved, so that the muscular disability and the requirements of prostigmine soon were about the same as before the onset of the infection. Sulfanilamide appeared to have had no effect on the myasthenia gravis, aside from that resulting from the control of the pharyngitis.

The patient continued to improve slowly, and on March 17 she was discharged with instructions to take 15 mg. of prostigmine bromide orally three times a day. With this medication the course was fairly satisfactory for about a month. About two months after her discharge from the hospital, the patient required increasing doses of prostigmine. The amounts of the drug were increased gradually until as many as 10 tablets of prostigmine bromide, each containing 15 mg., were taken daily. During the five months preceding her fourth admission to the hospital, on March 11, 1940, hypodermic administration of prostigmine methylsulfate was necessary on occasions when no improvement in muscular weakness was obtained with oral administration of the tablets.

Examination at the time of the patient's fourth admission showed definite weakness and easy fatigability of the muscles of the face and extremities. There was ptosis of both lids, and all the extraocular movements were moderately limited.

Course in the Hospital.—For four weeks the patient was given prostigmine bromide without any other form of medication, and during this period a study of the vaginal smears demonstrated that the menstrual cycle was normal. On the first day of the menstrual period the patient noticed an increase in muscular disability, but during and immediately following it there was some improvement in the symptoms. Despite these changes the administration of prostigmine bromide was kept constant at 10 tablets of 15 mg. each daily, given by mouth. The fact that the patient remained in bed during this period is significant, inasmuch as she always finds it necessary to increase the dose of prostigmine on the first day of the menstrual period if she engages in her usual activities. During the fifth week of her stay in the hospital she was given 1,000 units of estradiol benzoate (progynon B) intramuscularly each day for four days. There was distinct exacerbation of muscular disability. On one occasion the subcutaneous administration of prostigmine methylsulfate was required because of respiratory distress. During the sixth and seventh weeks the patient was given testosterone propionate in doses of 10 mg. daily by intramuscular injection. A total of twelve injections was given. There appeared to be a slight, but definite, effect on the muscular symptoms in that the disability was less although the administration of prostigmine was unchanged.

The patient was discharged on May 11 on a regimen of limited activity at home and oral administration of prostigmine bromide, 30 mg. four times daily. Menstruation was delayed for about eight days, probably as a result of the testosterone propionate that had been given during the hospitalization. During this menstrual period the patient felt much improved.

On a subsequent occasion her local physician prescribed phenobarbital, in amounts of about 30 mg. three times daily. On the days on which the sedative was taken it was necessary to increase the amounts of prostigmine bromide from 7 to 12 tablets of 15 mg. each in order to maintain the functional capacity of the muscles at a constant level. The patient weighed 50 Kg.

CASE 10.—An American woman aged 22, unmarried, who was employed as a cashier, entered the New York Hospital on June 21, 1937, complaining of mus-

cular weakness. Five years before her admission the patient noticed weakness of the left arm. Shortly after the right arm began to tire readily after exertion. The weakness of the arms continued up to the date of her admission to the hospital, but varied in severity from time to time. Two years before her admission she began to have diplopia and ptosis. The diplopia was only occasional, but the ptosis occurred almost daily. These symptoms were more severe during the first few days of the menstrual period.

Examination disclosed the muscular weakness and fatigability of which the patient complained. There were definite ptosis on the left side and moderate impairment in the movements of the forehead and face. The extraocular movements were normal. With repeated activity the muscles of the extremities fatigued rapidly.

Subsequent Course.—The patient was followed in the outpatient department until Sept. 20, 1937. On that date she was admitted to the special research ward, where she remained until Feb. 7, 1938. During this period daily investigations were made on the effects of various substances, including prostigmine, physostigmine, pilocarpine, guanidine and several vitamin preparations. Determinations of the choline esterase activity of the serum were made daily.

Since her discharge from the hospital the patient has been taking 30 mg. of prostigmine bromide orally three times daily. Under this regimen she has had to limit her activity only slightly, except during the first few days of the menstrual period. At these times muscular weakness and fatigability usually are exacerbated and activity has to be restricted more definitely.

Myasthenia Gravis Associated with Psychoneurosis.—CASE 12.—A married man aged 28, a physician, entered the New York Hospital on Jan. 23, 1939, complaining of diplopia and generalized muscular weakness of six months' duration. In June 1938 he noticed difficulty in rising on his toes while playing tennis. A few weeks later he began to have slight blurring of vision, which shortly afterward developed into definite diplopia. At first the diplopia occurred only occasionally, but shortly it increased in frequency to the point at which it was practically constant.

About five months before his admission the patient began to tire easily after moderate activity. At about this time his wife noticed that his jaw drooped slightly and that the facial expression was less lively than before. One month later he began to take prostigmine on his own initiative and noted definite improvement in muscular function when the drug was used. In December 1938 he entered another hospital in New York city, where the opinion was expressed that the symptoms were due to a psychoneurosis and not to myasthenia gravis. One month later the patient entered the New York Hospital. Examination disclosed weakness of the facial muscles, slight ptosis on the left side and definite weakness and fatigability of the muscles of both upper extremities.

Subsequent Course.—During his period of hospitalization the patient frequently had considerable muscular weakness and fatigability. Faradic stimulation of various muscles induced fatigue more easily than is seen in normal subjects. The administration of 1 mg. of prostigmine methylsulfate subcutaneously was followed by definite improvement in muscular function. When 2 mg. of the drug was given subcutaneously the serum esterase activity was decreased from a resting level of 2.83 to one of 1.48; the changes in esterase activity were accompanied by distinct clinical improvement. Even when the larger amount of prostigmine methylsulfate was given, some muscular disability remained, but, despite his insistence that he could not continue an assigned activity, he was able to do so satisfactorily when he was sharply urged.

The oral administration of 0.6 Gm. of quinine sulfate was followed by definite exacerbation of muscular weakness, and the patient complained of difficulty in swallowing. The quinine did not change the serum esterase activity.

The patient was seen by the consulting psychiatrist, whose formulation was as follows: "Although the patient has shown psychoneurotic manifestations for many years, it appears that intensification of his emotional symptoms at present is secondary to organic disease rather than primarily accountable for the whole picture."

The patient was discharged with instructions to take 15 mg. of prostigmine bromide orally three times a day and 25 mg. of ephedrine sulfate and 10 Gm. of aminoacetic acid daily. Under this regimen the patient has been able to live a fairly satisfactory life of restricted activity, but it is apparent that the emotional factors, for which there has been no opportunity for adequate treatment, make it difficult for him to adjust himself satisfactorily to his disability.

Psychoneurosis with Habit Spasm: Asthma Accentuated by Prostigmine.—CASE 15.—An unmarried woman aged 42, a school teacher, was referred to the New York Hospital with the diagnosis of myasthenia gravis and asthma. Two years before her admission to the hospital the patient began to make grimaces of the face and to close the eyes forcefully. At first she made these movements only occasionally, but they soon increased in frequency until they were repeated continually. The grimace and movements of the eyelids increased in severity and frequency whenever the patient felt tense or excited. She consulted a physician, who mistook the forceful closure of the eyes for ptosis. The diagnosis of myasthenia gravis was made, and prostigmine was prescribed. In all, about 1,500 ampules of the methylsulfate, each containing 1 cc. of a 1:2,000 solution (0.5 mg.), were administered by subcutaneous injection during the two years preceding the time of her admission. One year before her admission to the hospital the patient had an attack of bronchitis, which apparently cleared up. However, a short time later attacks of asthma developed. These attacks usually followed the administration of prostigmine. The patient noticed that the attacks of asthma were more frequent and more severe when prostigmine was taken. For the next year and until the time of her admission, all the symptoms increased in severity, making it necessary for the patient to discontinue her work.

There was no history of muscular weakness or fatigability. The past personal history revealed that during her childhood the patient frequently wet the bed and bit her nails. She was regarded by her family as being tense and apprehensive.

Examination showed frequent grimacing of the face. The eyes often were closed with considerable force, while the rest of the facial muscles were drawn up into a grimace. There was no muscular weakness or fatigability. Auscultation of the lungs revealed generalized prolongation of the expiratory breath sounds, a moderate number of asthmatic wheezes and numerous fine, moist rales throughout both lungs. The remainder of the examination revealed nothing remarkable. A roentgenogram of the lungs revealed parenchymal involvement.

Subsequent Course.—Prostigmine was discontinued. After the third day of the patient's stay in the hospital all signs and symptoms of bronchial asthma had disappeared. She was seen by the psychiatric consultant, whose diagnosis was psychoneurosis with anxiety. Although the asthmatic symptoms disappeared with almost dramatic suddenness, the improvement of the habit spasm of the face was gradual. It was felt that the large amounts of prostigmine probably had been an important factor in inducing the attacks of bronchial asthma.

Hoffmann-La Roche, Inc., Nutley, N. J. (R. D. Shaner, M.D., medical director) supplied prostigmine methylsulfate.

NEUROLOGIC SYMPTOMS FOLLOWING EXTENSIVE OCCLUSION OF THE COMMON OR INTERNAL CAROTID ARTERY

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Occlusion of the carotid vessels is not a rare lesion. Since the introduction of surgical treatment for pulsating exophthalmos, intracranial aneurysms and uncontrollable nasal hemorrhage by ligation either of the common carotid or of the common and internal carotid arteries, many cases with neurologic residua have been reported. However, the changes following surgical ligation rarely show the clearcut syndromes produced by the extensive spontaneous closure of these vessels. The operations are usually performed on young persons in whom the collateral circulation seems satisfactory, so that the loss of nerve tissue is kept to a minimum. Even in the most extensive ligation, as practiced by Dandy [1] and others,[1a] the length of the vessels occluded is not as great as that produced by sudden thrombosis or by an embolus with a long thrombus behind it.

When spontaneous closure of the carotid arteries on one side occurs, the thrombus may extend from the origin of the common carotid artery through the internal carotid, the ophthalmic and part of the middle cerebral artery. A plug of this size seriously limits the pathways for collateral circulation and produces a more constant anatomic lesion in the brain. Although the literature contains many references to results of occlusion of the carotid vessels, there are few reports of the typical syndrome, as found in man. It is our desire to present the clinical picture with the neurologic findings in 3 chronic cases that have come

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1. Dandy, W. E.: The Treatment of Carotid Cavernous Arteriovenous Aneurysms, Ann. Surg. **102**:916 (Nov.) 1935.

1a. Fetterman, J. L., and Pritchard, W. H.: Cerebral Complications Following Ligation of Carotid Artery, J. A. M. A. **112**:1317 (April 8) 1939. Marinesco, G., and Kreindler, A.: Oblitération progressive et complète des deux carotides primitives; accès épileptiques; considérations sur le rôle des sinus carotidiens dans la pathogénie de l'accès épileptique, Presse méd. **44**:833 (May 23) 1936.

under our observation. All present the same features, differing only in the presence or absence of aphasia, which of course is determined by the side of occlusion.

REPORT OF CASES

CASE 1.—J. P., a boy aged 7 years, was admitted to the Harriet Lane Home, Johns Hopkins Hospital. The family and past histories were noncontributory. The present illness began six months before his admission, when he had pneumonia of two weeks' duration. A "crisis" occurred about five days after the appearance of his fever, and from then on convalesence seemed uneventful. About three weeks after the onset of the pneumonia the boy began to complain of severe headache, which lasted for several days. Once during this period he experienced epigastric pain. Then one day he said his right arm "tickled." A few moments later he fell unconscious. There were no convulsions or clonic movements.

His father, who was intelligent and quick-witted, stated that he could feel no pulse at the right wrist but that there was a good pulse at the left wrist. This was confirmed by the family physician, who arrived shortly after the accident. Within a few hours the boy regained consciousness. It was then evident that he had complete left hemiplegia, with paralysis of the facial nerve of central type. He was unable to swallow liquids without strangling and coughing. Fluids were regurgitated through the nose.

A few hours after the cerebral accident the radial pulse returned to the right wrist. After regaining consciousness, the child gradually improved. Strength returned slowly, and at the end of two months he was able to stand with support. About this time it was noticed that his right eye would often show a squint. By the time of examination, about six months after the onset of the illness, the boy was able to walk unaided without difficulty.

Physical Examination (Dr. Frank R. Ford).—The child was well developed and well nourished. He was intelligent for his age and cooperated well. No arterial pulsations could be felt in the right side of the neck. The right pupil was larger than the left and did not respond to the stimulation of direct light but reacted well consensually. The right eye was completely blind. Vision was normal in the left eye, and no field defects could be demonstrated. This was confirmed by perimetric studies. Ophthalmologic examination showed a small chalk-white disk on the right; the retinal arteries were reduced to minute threads, and the veins were only a little larger. The retina was atrophic and thin. No abnormalities were seen in the left eye. The external ocular movements were of full range. Nystagmus was not present, but there was a nonpersistent squint during which the right eye deviated outward. Typical paralysis of the left facial nerve of central type was present. The remainder of the cranial nerves showed no abnormality.

Moderate paresis of the left extremities and mild spasticity of the left arm were noted. There was partial loss of individual finger movements, but the hand grips were of almost equal strength. Voluntary movements at the shoulder, elbow, wrist, hip and knee were of good strength and range. The gait was characteristic of mild left hemiplegia. Station was steady; no tremor or ataxia was noted. Speech was normal. No sensory disturbances could be demonstrated.

The tendon reflexes were increased on the left, but the abdominal reflexes were diminished. Clonus and the Hoffman reflex were not elicited. Plantar stimulation caused a variable response, but at times a positive Babinski reflex was observed.

Impression.—The diagnosis was thrombosis of the right common and internal carotid arteries, with occlusion of the ophthalmic artery and partial occlusion of the right subclavian artery.

What part the pneumonia played in the process is difficult to say. The case, however, is almost exactly similar to case 3 reported by Hyland.[2] The patient showed the minimal symptoms that would be expected from such a massive thrombosis.

Case 2.—M. B., a woman aged 52, was admitted to the Baltimore City Hospitals on March 28, 1933 with obvious hemiplegia involving the right side of the body. She had had a "stroke" involving the left side four years previously, but most of the sequelae had disappeared.

Four days before admission she suddenly became unconscious, and paralysis of the right side of the body developed. Since the accident she had been unable to speak. The length of the period of unconsciousness at the time she was stricken was not accurately determined.

On arrival at the hospital the patient was conscious and fairly cooperative. She seemed intelligent but was unable to talk. Results of the general physical examination were normal except that the carotid pulse could not be felt on the left side. The blood pressure was 70 systolic and 40 diastolic.

The neurologic examination revealed complete right hemiplegia. The left pupil was larger than the right and reacted very slowly to light, but responded promptly when light was directed into the right eye. Vision in the left eye was restricted to recognition of bright lights. The left optic disk was pale, and the arteries were small. No abnormalities were seen in the right fundus. There was weakness of the right facial nerve of central type. Swallowing was accomplished with difficulty. The tongue protruded to the right. Speech was unintelligible due to motor aphasia. Pain, touch and temperature sensations were not as well appreciated over the entire right side of the body as over the left. The tendon reflexes were overactive and the Babinski response was positive on the right side. Clonus and the Hoffmann reflex were not present. Because of the history of a previous stroke it was thought the patient probably had pseudobulbar palsy.

Studies of the blood and urine gave normal results. The Wassermann reactions of the blood and spinal fluid were negative.

The impression was that of thrombosis of the left internal carotid artery.

Reexamination in May 1939 revealed complete primary atrophy of the left optic nerve. The left eye was blind (fig. 1). Palsy of the right facial nerve was still present. The right arm was spastic and was held in a typical hemiplegic position. The fingers were contracted in flexion. The right leg was spastic and was held externally rotated and slightly flexed at the knee. The patient was unable to walk. The reflexes and diminution of sensation remained as before. Loss of two point discrimination and astereognosis were present on the right. Speech was little impaired; aphasia was not demonstrated, but the patient had to speak slowly in order to pronounce words. Memory was poor. The blood pressure was 130 systolic and 90 diastolic.

Case 3.—T. T., a Negro aged 60, was first seen in the outpatient department of the Johns Hopkins Hospital on May 11, 1934, where the following history

2. Hyland, H. H.: Thrombosis of Intracranial Arteries, Arch. Neurol. & Psychiat. **30**:342 (Aug.) 1933.

was obtained: In 1909, when he was 29, he was shot in the chest, and for the next year often coughed up small amounts of blood. At the age of 47 he had a penile lesion.

The complaint at the time of admission to the dispensary was coughing and a sensation of choking. About six months before, while working in the heat, he acquired a chronic cough. Large amounts of thick, heavy sputum were expectorated, but it was never blood tinged.

Physical examination revealed increased retromanubrial dulness and a tracheal tug. As shown by percussion, the maximum diameter of the heart, in the left fifth interspace, measured 15 cm. No murmurs were heard. The radial pulses were equal and of good quality. The vessel walls were thickened. The blood pressure was 136 systolic and 88 diastolic. The results of neurologic examination were negative. The Wassermann reaction of the blood was positive. A roentgenogram of the chest showed a shadow which was interpreted as an aneurysm of the innominate artery. A bullet was seen in the soft tissues in the left apex of the thorax (fig. 2).

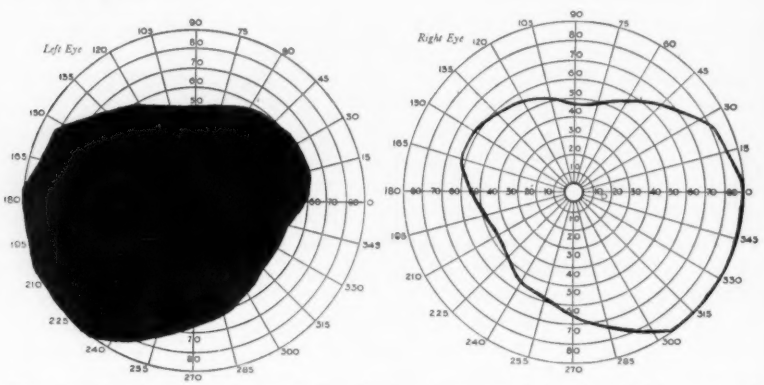

Fig. 1.—Visual fields in case 2. Vision is normal in the right eye and is limited to pupillary reaction in the left eye.

The patient was referred to the syphilis clinic and was followed three years. A note on June 11, 1934 stated that the pupils were small and irregular but that they reacted well to light and in accommodation. The visual fields were normal. At this time it was first observed that the fingers of the right hand showed moderate clubbing. Another note stated that vibratory sense was absent in the legs. Neurologic examination in 1936 revealed that the tendon reflexes could not be elicited at the ankles and were obtained with difficulty at the knees. Position sense was absent in the toes. Gait and station were normal. Examination of the eyes disclosed no further abnormalities. The Wassermann reaction of the cerebrospinal fluid was reported as negative.

On Dec. 27, 1937 the patient was admitted to the Baltimore City Hospitals. He had worked as a stevedore until the previous day. About 2:00 a. m. on the day of admission he had a violent period of coughing, and a few minutes later his left arm felt numb. When he attempted to stand, he found his left leg would not support him. Vision was greatly reduced, and he could scarcely see.

Physical examination on arrival at the hospital showed that the temperature was 98.8 F., the pulse rate 64, the respiratory rate 18 and the blood pressure 160

systolic and 120 diastolic. Breathing was stertorous and interrupted by frequent coughing. The pupils were unequal, the right being large and eccentric. The right pupil reacted poorly to light but well consensually. The right retinal arteries were very small.

There was weakness of the left facial nerve of central type, and the tongue protruded to the left. Tendon reflexes were sluggish on the right and absent on the left. The Babinski reflex was present bilaterally. Speech was thick and dysarthric.

Laboratory Examination.—Studies of the blood, urine and stool gave normal results. The Wassermann reaction of the blood was positive. Lumbar puncture revealed a pressure of 200 mm. of water and 129 crenated red blood cells and 7 white blood corpuscles per cubic millimeter of cerebrospinal fluid.

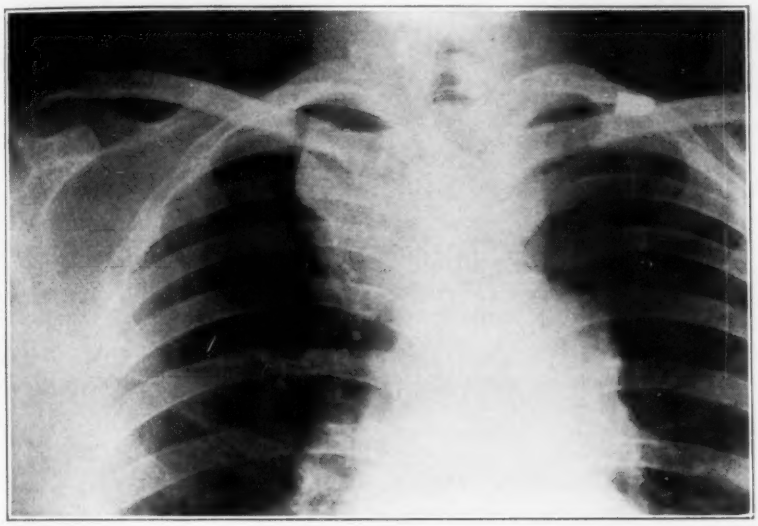

Fig. 2.—Roentgenogram of the chest in case 3. A smooth spherical mass can be seen in the upper right side of the chest, which is an aneurysm of the innominate artery. A bullet is present in the soft tissues in the left side of the neck.

A few days later it was demonstrated that the patient was blind in the right eye. The disk showed marked pallor. An increase of flexor tone was noted in the left arm. Finger movements of the left hand were poorly performed. General hypalgesia of the left side was found. Over the entire left side of the body there was a small amount of edema. The Babinski response could not be demonstrated. Bilateral ataxia of the legs was present.

Improvement was slow, and vision remained poor. Speech was recovered completely before discharge, on April 11, 1938.

On May 13, 1938 the patient returned to the City Hospital. During the interval he had regained some use of his left leg and was walking again. On the day of admission he had a convulsion, which started on the left side of the face, spread over the entire left side of the body and finally involved the right leg. There was no loss of consciousness.

Neurologic examination demonstrated that the facial palsy remained. The left arm was spastic in flexion. Voluntary motion was very poor, and ability to perform fine movements with the left hand was lost. The left leg showed no abnormality in tone, strength or voluntary movement, except for the ataxia. The pupils and fundi were unchanged. Pain and touch were diminished over the left side of the body and could not be localized on the left side of the face and

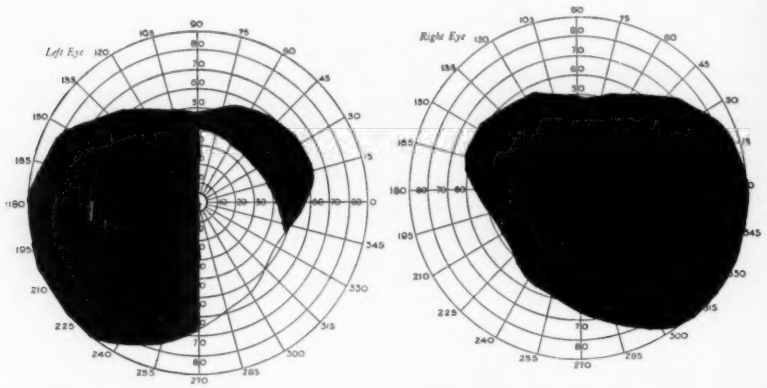

Fig. 3.—Visual fields in case 3. The right eye is blind, and the pupil is fixed to light. There is temporal hemianopia in the left eye, due to injury to visual pathways in the right cortex. The defect in the nasal field is probably due to poor cooperation.

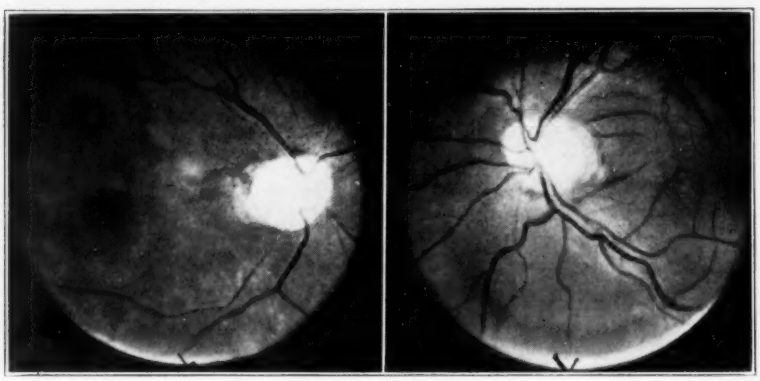

Fig. 4.—The fundi in case 3. Note the extremely small caliber of the arteries and the sparse vascular pattern in the right fundus. The disk has atrophied, and the retina has disappeared in the macular region. The picture is of one thrombosis of the central retinal artery. The fundus of the left eye is normal.

the left arm. Position sense, two point discrimination and stereognosis were absent in the left arm. Tendon reflexes were overactive in this arm. The patellar reflex was absent on both sides, but the left ankle reflex was present. Hoffmann and Babinski reflexes were elicited on the left. Gait was shuffling and was typical neither of hemiplegia nor of tabes dorsalis.

Reexamination in August 1938 for the first time demonstrated temporal hemianopia on the left (fig. 3). The right eye was completely blind. Photographs of the fundi are seen in figure 4; the atrophic macula in the right eye may be observed in the photograph on the left. The right pupil did not react to light directly but constricted well consensually. The left pupil reacted normally. No pulsations could be felt along the course of the right carotid artery. Otherwise the condition was unchanged.

The large aneurysm of the right innominate artery was undoubtedly the source of an embolus. In this case the function of the anterior cerebral artery was spared, as was the circulation about the internal capsule. The convulsion was due to the irritation of the cortical scar.

COMMENT

In the cases just cited a similar group of neurologic changes are shown. Cases of less severe symptoms following surgical occlusion of the carotid arteries in young persons are described in the literature. In fact, in many cases no abnormalities occur, not even blindness, when the internal carotid artery is ligated both in the neck and intracranially. Usually the collateral circulation is tested before operation, and the procedure is carried out only if the patient can tolerate the ligation. The actual segment of artery which is isolated is rather short, and collateral circulation on the same side can be established quickly. In the cases reported by Chao and associates [3] the syndrome was not clearcut, and, from the history given, the occlusion probably developed slowly, allowing time for the establishment of a degree of collateral circulation.

Another factor which causes variation in the extent of the symptoms is the size of the connecting vessels in the circle of Willis. Normally most of the blood circulating in the anterior cerebral artery comes from the internal carotid artery on the same side. If the anterior communicating artery connecting the two anterior cerebral arteries is large, the circulation in the anterior cerebral artery should not be greatly affected by homolateral ligation of the carotid artery. Also, the posterior communicating arteries of the circle of Willis, together with a rather rich anastomosis of the branches of the middle cerebral artery with those of the anterior and posterior cerebral arteries, may supply a fairly adequate stream of blood to the branches of the middle cerebral artery after ligation of the carotid artery. When these anastomoses are large and plentiful or when they are given time to enlarge, the area of cerebral softening following the slow occlusion or ligation of the carotid vessels may be small, or even negligible. Should the connecting vessels in the circle of Willis be small or absent, much more widespread changes would occur in the cortex.

3. Chao, W. H.; Kwan, S. T.; Lyman, R. S., and Loucks, H. H.: Thrombosis of the Left Internal Carotid Artery, Arch. Surg. **37**:100 (July) 1938.

The degree of aphasia, the loss of sensation on the hemiplegic side of the body and the field defect in the contralateral eye all seem to depend largely on the extent of the cortical softening in the region supplied by the middle cerebral artery. As many of the areas subserving speech are in the posterior portion of the parietal lobe, where they are supplied by small branches of the middle cerebral artery, overlap with branches from the posterior cerebral artery is quite variable. The precise amount of aphasia in any particular case will be dependent largely on this overlap and on the anastomosis of small branches of the two arteries. The amount of softening that occurs in the optic radiation is dependent on intactness of the anterior choroidal artery and the deep branches of the middle cerebral artery. Some patients have no aphasia, field defect in the contralateral eye or anesthesia on the hemiplegic side, but if the blood supply from the neighboring and collateral vessels is small, extensive aphasia, marked hemiplegia, hemianesthesia and hemianopia may follow. Any of these symptoms may show all gradations, depending on the local vascular anastomoses and the extent of occlusion of the middle cerebral artery.

No attempt has been made in this paper to cover the entire literature. The cases cited are clearcut examples of the clinical findings in chronic patients who have suffered massive occlusion of the carotid arteries on one side. Three of the most usual causes of occlusion are represented in the cases described here, namely, infection, arteriosclerosis and embolus from an aneurysm. References to a few articles are included for those who care to examine the literature more thoroughly.

SUMMARY

Occlusion of the carotid artery produces atrophy of the optic nerve and loss of vision in the eye on the same side, due to closure of the ophthalmic artery. The circulation is also impaired in the anterior choroidal, anterior cerebral and middle cerebral arteries, which are terminal branches of the internal carotid artery. There may occur softening of the brain, which is usually maximal in the field of the middle cerebral artery. Temporal hemianopia, due to involvement of the optic radiation, may be present in the visual field of the opposite eye. Contralateral hemiplegia and hemianesthesia, more marked in the face and arm than in the leg, also result; they appear to be due to cortical destruction rather than to injury to the internal capsule. If the left cortex is involved in a right-handed person, there may be a variable degree of aphasia. Dysarthria and dysphagia are often present during the first few days after the vascular occlusion, but disappear later.

A NEW METHOD FOR TREATMENT OF CYSTIC CRANIOPHARYNGIOMA BY INTRA-VENTRICULAR DRAINAGE

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NEW YORK

A new method for the treatment of suprasellar cysts, by internal drainage into the cerebral ventricles, is herewith described.

In the past it has been the almost universal practice to expose these lesions by way of a subfrontal approach to the chiasm, the cyst usually presenting itself just beneath the chiasm and between the two optic nerves. A small opening would be made through the cyst wall at this point, and the contents of the cyst drained across the shallow cisterna chiasmatica and into the extra-arachnoid (subdural) space.

Early recurrence was the rule after this method of treatment. The reason for this is clear, since the operation provided no way of disposing of the secretions which continued to be elaborated from the inner surface of the evacuated cyst. The drainage opening through the wall of the cyst was of necessity small, since its size was limited by the optic nerves and optic chiasm. Many structures tended to occlude this small opening, often almost immediately, such as damaged strips of torn arachnoid membrane or the overlying frontal lobe, but especially small postoperative blood clots, which are almost unavoidable. Furthermore, the contents of the cyst were highly irritating to the meninges and tended to set up an inflammatory reaction, ending in masses of adhesions in the vicinity of the chiasm, which acted to seal off the new opening and to obliterate the pia-arachnoid space forming the chiasmatic cistern. Under these circumstances the secretions which actually did escape from the cyst found themselves in the extra-arachnoid (subdural) space from which there was no natural method of removal. As a rule, the surgical opening made through the wall of the cyst closed quickly, so that secretions subsequently elaborated within the cyst were retained there. Eventually, therefore, as the secretions accumulated, the cyst again reached its preoperative size and tension and again produced its characteristic pressure effects. Surgical drainage would again become necessary, but no

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sooner would the cyst be evacuated than it would once more begin to refill; and the vicious cycle would be repeated again and again, until blindness and exhaustion overtook the victim.

A new method for the operative treatment of suprasellar cyst is here described which utilizes a surgical principle in the treatment of this condition not heretofore employed, viz., the internal drainage of the cyst directly into the cerebral ventricles. The advantage of this method is that it provides a permanent means of disposing of the secretions which continue to be elaborated by the inner linings of the suprasellar cyst throughout the remaining lifetime of the patient. This is done by flushing out the cystic cavity with cerebrospinal fluid, which carries away the secretions, much diluted, in the regular cerebrospinal fluid circulation, and permits of their absorption along with that fluid by a physiologic mechanism.

TECHNIC OF THE NEW METHOD

A transfrontal osteoplastic flap is turned up in the usual way. A small incision is made through the posterior part of the middle frontal convolution, exposing the anterior horn and the body of the lateral ventricle. Here, anterior to the foramen of Monro, and close to the midline, will be seen, if the case is well chosen, a rounded elevation on the floor of the ventricle as it is pushed upward by the top of the underlying cyst (fig. 1). This relation of the underlying suprasellar cyst to the floor of the lateral ventricle is verified by means of puncture with a ventricular needle through the floor of the ventricle and into the cavity of the cyst.

A small circular opening is then made through the floor of the ventricle along the needle tract and carefully enlarged until it is about 2 cm. in diameter. It should be emphasized that this must be done with a small blunt dissector, using only the gentlest force to avoid injury to large blood vessels lying between the brain and the cyst. If the case has been properly selected for this method of treatment, the opening will be made through the attenuated subcallosal gyrus, which forms the mesial part of the floor of the ventricle in this region and is only 2 or 3 mm. in thickness, and no trauma whatever will be suffered by the head of the caudate nucleus or by any of the other basal ganglia (fig. 2).

The top of the craniopharyngioma will now present through the opening in the floor of the ventricle. As much of its upper surface as possible is exposed and cleared off. The cyst is then incised and its contents are evacuated, after which the hole in the dome of the cyst is enlarged until it corresponds in size to the hole in the floor of the ventricle.

During the actual drainage of the cyst precaution should be taken to prevent escape of the contents of the cyst into dependent parts of the ventricular system, since, in concentrated form, this material is apt to be irritating to the ependyma. After the complete evacuation of the cyst has been made with the aid of the sucker, the cystic cavity should be repeatedly flushed out with physiologic solution of sodium chloride until the washings are returned quite clear.

The essential features of the operation are thus completed. In closing, the dura is sutured tightly, with careful approximation of the edges. The other steps in the closure are carried out in the usual manner.

REPORT OF CASES

The following cases illustrate this method.

CASE 1.—J. D., a man aged 22, was admitted to the New York Post-Graduate Hospital on Nov. 14, 1933, having been referred by Dr. Matthew Shapiro. The

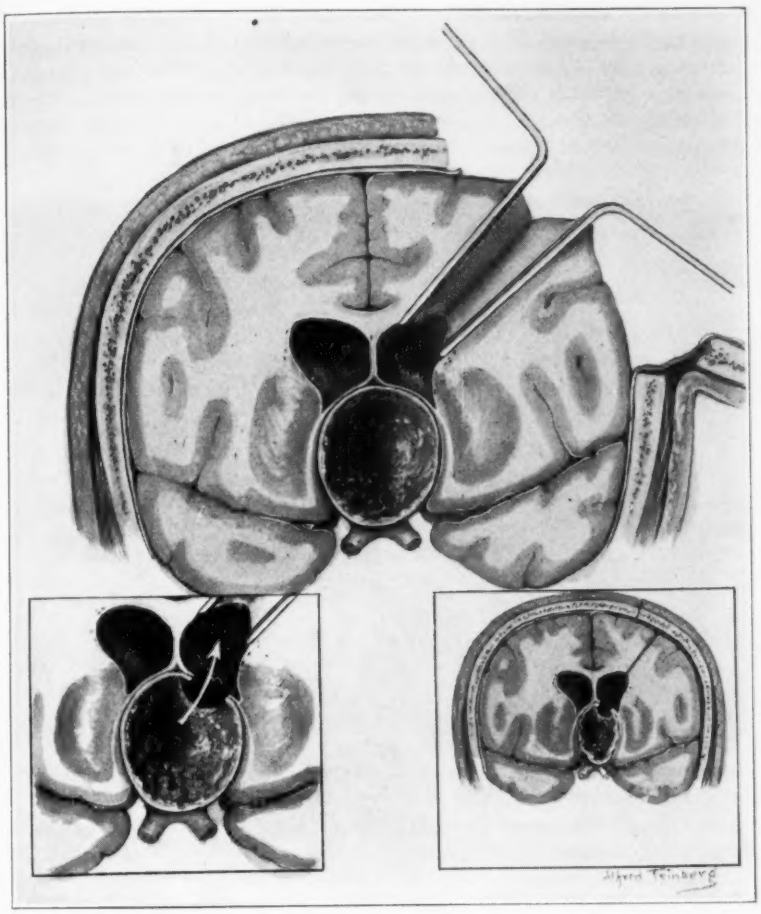

Fig. 1.—Technic of intraventricular drainage of craniobuccal cysts. Center: The frontal horn of the dilated lateral ventricle is entered through a small transcortical incision in the posterior part of the middle frontal convolution. The floor of the ventricle is seen to be pushed upward by the dome of the cyst. Lower left corner: An opening is made by blunt dissection through the floor of the ventricle and the dome of the underlying cyst. In typical cases this opening is anterior to the foramen of Monro and close to the midline, passing through the thin, flat subcallosal gyrus and completely sparing the head of the caudate nucleus. Lower right corner: After evacuation of the cyst its wall collapses. This relieves the pressure which the cyst when distended exerted against the optic chiasm, the foramens of Monro and the third ventricle. After the operation the cyst continued to drain into the ventricle.

patient complained of headache, failing vision, impairment of memory and mental reactions, nausea and vomiting and spells of intense subjective feelings of warmth without hyperthermia.

The patient was almost a dwarf, standing only 5 feet (152.5 cm.) high and weighing only 80 pounds (36.3 Kg.), but otherwise exhibiting perfect physical proportions. He was beardless. His voice was that of a boy. He looked sick as he lay in bed, complaining of headache, nausea and vomiting. Visual acuity was essentially normal in each eye, but there was practically complete right homonymous hemianopia. The temporal half of each optic disk was pale and the margins were sharp, whereas the nasal half of each disk was injected, the margins were indistinct and the veins leading from this region tortuous. The nasal half of each disk showed a measurable elevation of about 1 D. The appearance of the fundi suggested beginning papilledema superimposed on an older, low grade

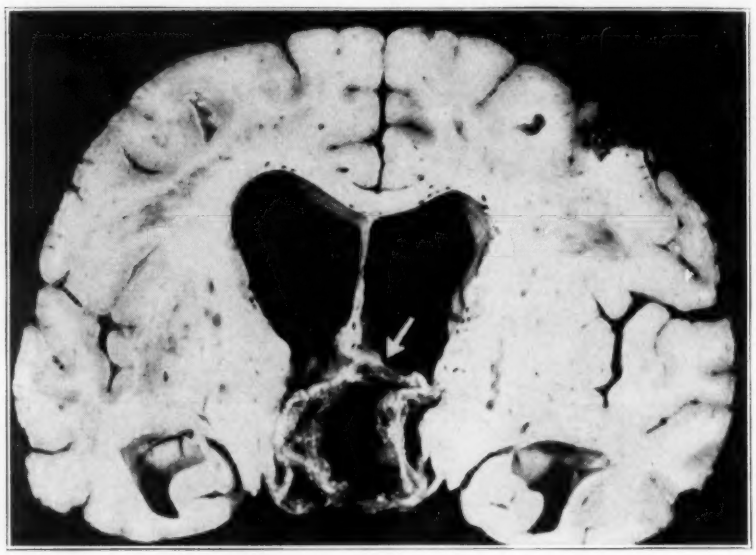

Fig. 2.—Coronal section through a medium-sized craniobuccal cyst and the brain just anterior to the fornix.

Intraventricular drainage is established through the medial part of the floor of the ventricle anterior to the foramen of Monro, in the region of the subcallosal gyrus.

The floor of the ventricle is thin at the point where the communication is made. It should be noted, also, that the basal ganglia are displaced laterally by the expanding cyst and are not damaged during the operation.

primary atrophy. There was slight right hyperreflexia. Roentgenograms of the skull showed suprasellar calcification typical of craniopharyngioma. The basal metabolic rate was —27 per cent. On the basis of the symptoms and the various findings, a diagnosis of craniopharyngioma was made.

Operation.—A left transfrontal osteoplastic bone flap was turned up on November 22. The dura was tense. Attempts to relieve this pressure by tapping the ventricle through a small opening in the dura were unsuccessful for the reason

that the ventricle could not be located, and this was taken to indicate that it was compressed or displaced. As the dura on the under surface of the frontal lobe was stripped away from the bone, great difficulty was encountered in retracting the brain, due to the excessive tension of the dura and the enclosed brain. Suddenly, however, there was a striking release of this intradural tension, so that almost without effort easy retraction of the dura as far as the sphenoid ridge and the posterior end of the olfactory groove was obtained. At this time no explanation of this sudden release of tension could be given.

The dura was opened along the sphenoid ridge and the optic chiasm brought into view without difficulty, but no cyst was visible. A needle was then introduced through the cortex in the direction of the suprasellar calcification revealed in the roentgenograms, and at a depth of several centimeters it seemed to pass through a wall and into a cystic cavity. From the needle there then escaped, a few drops at a time, about 2 or 3 cc. of a slightly icteric fluid, having the general consistency of spinal fluid but carrying in suspension a number of small refractive particles, which under the microscope proved to be typical cholesterol crystals, capable of polarizing light. Nothing more was obtained. The operator felt that nothing further should be done at this time and thereon closed the wound in the usual manner.

After the operation all the patient's symptoms and neurologic signs, except the evidences of physical and sexual underdevelopment, completely disappeared, and he was discharged from the hospital on December 10 in excellent condition. Shortly after his discharge he returned to his previous occupation as a filing clerk in a large business office, and he worked steadily at this employment, without losing a day because of illness, for over six and a half years (fig. 4 *A*).

Early in the summer of 1940 he experienced a short, transient bout of bifrontal headache, associated with visual disturbances which lasted approximately twenty-four hours and then cleared up spontaneously and completely. A week or two later I examined the patient on recommendation of his family physician and found him to be free of symptoms and apparently in the best of health. The neurologic examination, including taking the visual fields with small test objects, revealed no evidence of either local pressure on the optic chiasm or of generalized intracranial pressure. At that time he was again working, and this he was advised to continue.

On the night of July 1, 1940 (during my absence from the city) the patient was brought to the Neurological Institute in a deep coma, from which he could not be aroused. An emergency trephination and ventricular tap were performed at once by the surgeon in charge, pending fuller information about the patient. The ventricular fluid was under greatly increased pressure; this was reduced by withdrawal of a considerable quantity of fluid, but in spite of this the patient never regained consciousness and died before morning. Permission for an autopsy, unfortunately, could not be obtained.

Evidence indicated that this patient was suffering from a large cystic craniopharyngioma at the time he was first operated on, in 1923. It seems reasonably certain that in the effort to obtain adequate exposure of the optic chiasm at operation, the pressure of retraction transmitted through the overlying cortex to the tense (and presumably thin-walled cyst) caused it to rupture spontaneously into the ventricular system. That such a rupture under the pressure of retraction is entirely possible is

proved by the spontaneous rupture of a similar cyst under the eyes of the operator in the first operation on the second patient of this series (R. L.).

As weeks, then months and, finally, years went by without any return of symptoms indicating refilling and distention of the presumed suprasellar cyst, I was forced to the conclusion that the communication provided by accident between the cyst and the ventricular system had provided the patient with a better result than would have followed treatment by the common method of evacuating such a cyst, namely, by incising the wall in the vicinity of the optic chiasm and emptying it into the physiologically inert subdural space. This led me to seek a surgical method for draining suprasellar cysts into the ventricular system and resulted in the various experiences herewith recounted.

Case 2.—R. L., a boy 13 years of age, was admitted to the surgical ward of the Neurological Institute on Aug. 8, 1934, with a three months' history of failing vision and recent symptoms of generalized intracranial pressure. Three weeks before admission he had become totally blind in the right eye, and three days before admission he became totally blind in the left eye.

At the time of admission examination revealed obesity, with a typical Fröhlich habitus, total blindness and pale optic disks. The results of neurologic examination were otherwise essentially unimportant. The patient was suffering with severe headache, nausea and vomiting. Suprasellar calcification was seen in the roentgenograms. The diagnosis of a craniopharyngioma, with secondary obstructive hydrocephalus, was made.

Operation.—A right transfrontal flap was elevated on August 9. The dura was tense and great difficulty was encountered in retracting it and the frontal lobe away from the floor of the frontal fossa, but eventually the dura was opened along the sphenoid ridge. While the operator was strongly elevating the frontal lobe in an effort to increase the exposure, the lower portion of the field in the vicinity of the chiasm was suddenly filled with thick yellowish fluid having the color and consistency of machine oil and containing fine particles refractive to light, which were subsequently proved by microscopic examination to be cholesterol crystals. Simultaneously with the appearance of this fluid, the tension of the brain, which the operator had been attempting to overcome with his retractor, became strikingly less, so that it was then very easy to expose and inspect the optic chiasm and the neighboring structures. This inspection revealed the wall of a craniopharyngioma visible between the optic nerves, with a ruptured wall, from which thick yellow fluid was still escaping. When the cyst had been entirely emptied and washed out with physiologic solution of sodium chloride, the operation was terminated and closure made in the usual manner.

The patient made a satisfactory postoperative recovery. He was for the time being relieved of his headaches, and immediately after operation he could recognize persons with his left eye. However, by the time he was discharged from the hospital, on September 1, he had again lost all vision in this eye, as well as in the right eye.

Second Admission.—The patient was admitted by me to the New York Post-Graduate Hospital on March 19, 1935, approximately six months after his dis-

charge from the Neurological Institute, complaining of total blindness, severe pain in the region of the right eye, increasing somnolence and a gain of 40 pounds (18 Kg.) in weight.

Examination showed the old right frontal craniotomy wound to be bulging and tense. The boy was totally blind, except for a questionable degree of light perception remaining in the right eye. The right pupil also was thought to respond slightly to strong direct stimulation with light, while the left pupil was believed to react consensually under the same circumstances, thereby seeming to confirm the statement of the patient that he could discern light with this eye. Other findings were of relatively no importance. The basal metabolic rate was —27 per cent. Roentgenograms of the skull showed a "ballooned-out" sella, with suprasellar calcification. The opinion was that the suprasellar cyst had refilled and become sufficiently distended to compress and occlude the foramen of Monro, thus creating again a state of obstructive hydrocephalus.

Ventriculograms showed a huge cyst rising high above the sella and displacing upward the floor of the lateral ventricle (fig. 3 *A, B*).

Second Operation.—On March 21 a left transfrontal craniotomy was performed. The region of the chiasm was exposed by means of a typical subfrontal approach. There were extensive adhesions and much scar tissue about both optic nerves and the chiasm. Between these structures, however, could be seen the wall of the craniopharyngioma. The operative wound previously made in it could not be identified. A new opening was made through the wall in the same region, with release of about 30 cc. of thin, canary yellow, opaque fluid, filled with a suspension of fine particles refracting light. After removal of this fluid, the opening was enlarged sufficiently to permit inspection of the inner wall of the cyst. This appeared white, smooth and glistening, with here and there atheromatous plaques, similar in appearance to those which are seen at autopsy on the inner surface of a sclerotic aorta.

Neutral indigo carmine (2 cc.) was injected at this point into the left lateral ventricle by means of a ventricular cannula passed from without through the middle frontal convolution.

A groove director was then bent in such a shape as to permit it to be passed freely beneath the chiasm and through the opening that had just been made in the cyst wall, and then upward until it came to rest against the dome of the cyst. Pressure was now exerted on the director in a direction and with sufficient power to force its end through the cyst wall. Immediately there appeared within the cyst large quantities of blue-stained cerebrospinal fluid. This could have come only from the left lateral ventricle by way of the openings punched through its floor and the wall of the cyst by the blunt dissector. No bleeding followed this puncture, and the patient suffered no general reaction as a result of it. After this closure was made by layers, without drainage.

The postoperative course was smooth. The next morning the patient felt well and enjoyed a full breakfast. His further recovery from the effects of the operation was rapid and uncomplicated, and he was discharged from the hospital, ambulatory, on April 11, the twenty-first postoperative day. His headaches and somnolence had disappeared, but his vision had not improved.

Third Admission.—The patient was readmitted to the New York Post-Graduate Hospital on May 10, 1936. After his last operation, performed on March 21,

1935, he had been free from headache and had felt well until about the middle of April 1936, a month before his admission to the hospital. Since then, however, headache had returned.

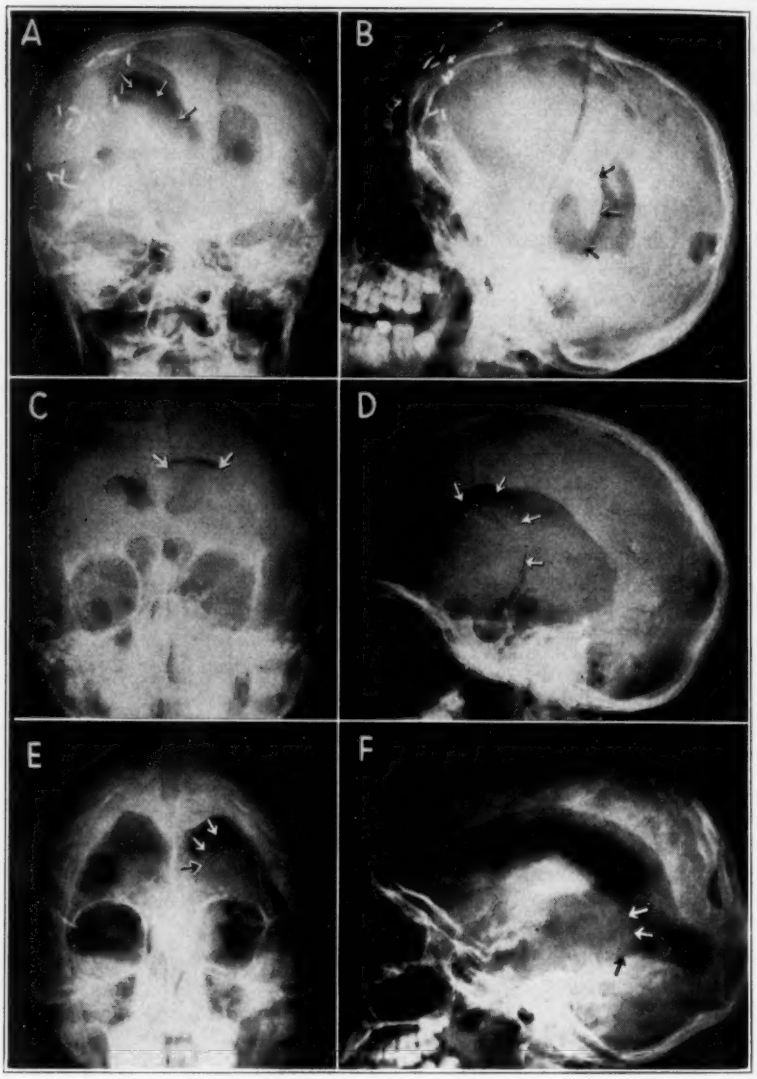

Fig. 3.—Ventriculograms showing the size, position and relation to the ventricles in 3 cases of craniopharyngioma in which intraventricular drainage was established. The arrows indicate the limits of the cysts. *A* and *B:* case 2 (fig. 4 *B*); *C* and *D:* case 4 (fig. 4 *D*); *E* and *F:* case 5 (fig. 5).

On examination, the various postoperative defects in the bone were found to be tense and bulging. Light perception was still present in the right eye. Otherwise the results of examination were essentially unimportant.

Third Operation.—On May 14 the old right transfrontal craniotomy wound was reelevated. The ventricle was tapped for relief of the extreme intradural tension, after which it was opened widely. After the dura had been reflected, a transcortical incision was made through the middle frontal convolution and into the anterior horn of the right lateral ventricle. The cerebrospinal fluid within the ventricle was colorless and thin, but was filled with a suspension of minute particles refracting light, which on microscopic examination proved once more to be typical lecithin crystals. In the floor of the ventricle, close to the midline and anterior to the foramen of Monro, which was compressed to a mere slit, was a domelike elevation measuring approximately 2.5 to 3 cm. from side to side and rising about 1 cm. above the general level of the ventricular floor. This occupied a position essentially above the sella. A ventricular needle was passed through the floor of the ventricle and into this dome-shaped structure, which proved to be a cyst. From this cyst was aspirated approximately 30 cc. of colorless fluid containing a large amount of whitish, opaque, lipoid and crystalline particles, having an appearance very similar to that of the cerebrospinal fluid found in the ventricle, only more concentrated.

Using a blunt dissector, so as not to cut any large blood vessels, a hole approximately 1 cm. in diameter was then cut in the floor of the ventricle, which at this point proved to be only about 2 to 3 mm. thick. This uncapped the dome of a large underlying cyst, which was closely approximated and loosely adherent to the brain. An opening was then made through the dome of this cyst, about 1 cm. in diameter, and the fluid remaining in the cyst removed with suction. At the end of this procedure there remained a wide open, free communication through the thinned-out floor of the ventricle and the dome of the cyst which connected these two cavities. The dura was closed tightly, and the skin and bone were replaced, without drainage.

The postoperative course was smooth and uncomplicated. The patient was out of bed on the tenth postoperative day and was discharged on the fourteenth day. At this time all feeling of intracranial pressure had disappeared, and the flap was not elevated. Unfortunately, however, there was still no return of vision.

Fourth Admission.—The patient was admitted to the New York Post-Graduate Hospital for the third time on Jan. 23, 1937. After his discharge from this hospital in May 1936 he had been essentially symptom free, except for his blindness, until January 10, approximately two weeks preceding the latest admission. At that time there had developed rather rapidly a severe frontal headache, which at times became so great that he screamed with agony and became almost maniacal as a result of the pain. Coincidental with these periods of headache, the bone flaps and decompressive areas resulting from the previous three operations became elevated and tense. These symptoms increased steadily during the two weeks ending with the patient's third admission to this hospital.

Examination of the patient at this time revealed essentially the same condition as on all other occasions, except at the old operative areas, where the presence of intracranial tension was strikingly manifest.

Ventriculograms, made on February 4, showed marked dilatation of the lateral ventricle and revealed a huge mass arising from the suprasellar region and extending posteriorly and to the right, finally ending in the atrium of the right lateral ventricle.

Fourth Operation.—A right temporoparietal craniotomy was performed on February 11. Again the dura was exceedingly tense and the ventricle had to be tapped before it could be safely opened. After this was done and the brain

exposed, an incision was made through the cortex in the neighborhood of the angular gyrus directly into the atrium of the right lateral ventricle. Here was seen the posterior end of a huge suprasellar cyst, projecting into the ventricle from before backward, like a large sausage. The entire end of this cyst was cut off, leaving an opening about 2 cm. in diameter between the cavity of the cyst and the cavity of the ventricle. The cyst was again seen to be filled with the same type of fluid and lipoid substance as that observed at the last operation. After this was thoroughly washed out, the operator could freely inspect the inside of the cystic cavity and could pass a probe directly down into the pituitary fossa. The operation was then terminated, and the wound closed in the usual fashion, without drainage.

The patient withstood the procedure well, and on the following day his general condition was excellent. He was alert and free from headache and partook generously of nourishment. Unfortunately, a troublesome postoperative infection developed in the incision in the scalp, which delayed for many weeks his discharge from the hospital. Eventually, however, the wound healed in satisfactory manner, and the patient was discharged (fig. 4*B*).

Four years have now elapsed since the patient's last operation, and he is still alive and in general good health. Although vision has never returned, he has been entirely free from the unbearable headache which led to the last operation. He is bright and alert and is fairly well adjusted to the fact that he cannot see.

This is the first case in which an attempt was made to establish, by various surgical means, permanent drainage of a suprasellar cyst directly into the cerebral ventricles.

Four distinct operative procedures were carried out on this patient: (1) the conventional incision of the wall of the cyst in the region of the chiasm; (2) drainage of the cyst into the ventricular system through an opening made by means of a "blind punch"; from the cavity of the cyst upward into the cerebral ventricle; (3) drainage of the cyst into the ventricle through an operative opening cut in the floor of the anterior horn of the right lateral ventricle and through the dome of the cyst under direct vision, and (4), in a subsequent operation, similar drainage through an opening in the posterior part of the cyst as it projected into the ventricle near the atrium.

After the first three evacuations of the cyst there was relatively rapid refilling, with return of symptoms of pressure within six, ten and six months, respectively. This would seem to indicate the time required for the secretions being elaborated continually from the tissues lining the cyst to completely refill and distend it. In view of the fact that more than four years have elapsed since the last operation without return of any symptoms of pressure, the conclusion seems justified that the last opening made between the cyst and the ventricle has remained patent, and that not only the cyst is secreting directly and continuously into the cerebrospinal fluid circulation but these secretions are being absorbed along with the cerebrospinal fluid.

Case 3.—C. G., a girl 8 years of age, was admitted to the neurologic service of Dr. Foster Kennedy at Bellevue Hospital in December 1935. At this time the patient gave a history of failing vision, headache, nausea and vomiting over a

period of eight months. A short time before admission there had been a marked increase in all symptoms. When admitted, she had been totally blind for several days and was in a semistuporous condition, from which she could be aroused only with difficulty. Examination supplemented with ventriculograms led to the diagnosis of craniopharyngioma.

Operation.—In January 1936 I performed a right frontal craniotomy and evacuated a large cyst in the conventional manner through an opening made in the cyst wall in the general region of the optic chiasm.

The child withstood the operation fairly well, and there was rapid general improvement but no return of her lost vision. She continued to be free from symptoms of intracranial pressure until April 1936, when she again began to have intermittent, recurrent bouts of headache, nausea and vomiting. These continued without much change until January 1937, when there was a marked increase in severity of the symptoms, associated with rather alarming stiffness of the neck and a tendency toward opisthotonos.

Second Admission.—The patient was admitted to the New York Post-Graduate Hospital in January 1937, because of the severity of the symptoms just described. There were extreme rigidity and dorsiflexion of the neck and a tendency toward opisthotonos. The patient alternated between states of stupor and states of excitement, when she cried with pain in her head. The optic nerve heads were pale, but the vessels were markedly congested and tortuous. She was totally blind. There were evidences of marked bilateral involvement of the pyramidal tracts. Otherwise the results of examination were essentially negative.

The impression was that the previously evacuated craniopharyngioma had refilled and had become distended sufficiently to include the foramens of Monro, thus creating acute hydrocephalus.

Second Operation.—On January 23 the old right transfrontal osteoplastic bone flap was reelevated. The dura was tense, and the ventricles had to be tapped before it was considered safe to open the dura. After this, however, a flap of dura was turned up which exposed the posterior part of the middle frontal convolution. An incision through the cortex was then made in this convolution and the ventricular cavity exposed and emptied of cerebrospinal fluid.

The foramen of Monro on the right was seen to be widely dilated, and filling it and tending to herniate through it from the third ventricle into the lateral ventricle was the relatively thin, reddish wall of a cyst. This wall was then incised at the point where it protruded through the foramen of Monro, with an immediate gush of clear fluid. A larger piece of tissue was then cut away from the wall of the cyst until the opening from the lateral ventricle into the cyst was approximately 1 or 1.5 cm. in diameter. Free communication was established between the two ventricles by cutting a large window in the septum pellucidum. Closure was effected in the usual manner by layers of tissue and without drainage. Microscopic examination of the tissue removed showed irregular clefts lined by layers of cuboidal cells, in some places as many as eight or ten layers. The cells had an appearance suggestive of ependymal cells.

The postoperative course was smooth and uneventful. The patient left the hospital on February 20. Except for her blindness, she was entirely symptom free.

Approximately four years have now elapsed since intraventricular drainage was established in this child. During this interval there has been no evidence of recurrence of intracranial hypertension. The patient is a regular attendant at the New York School for the Blind and has become a proficient reader of Braille. In spite of her tremendous handicap of blindness, she continues to be an alert, cheerful and very superior little girl (fig. 4 *C*).

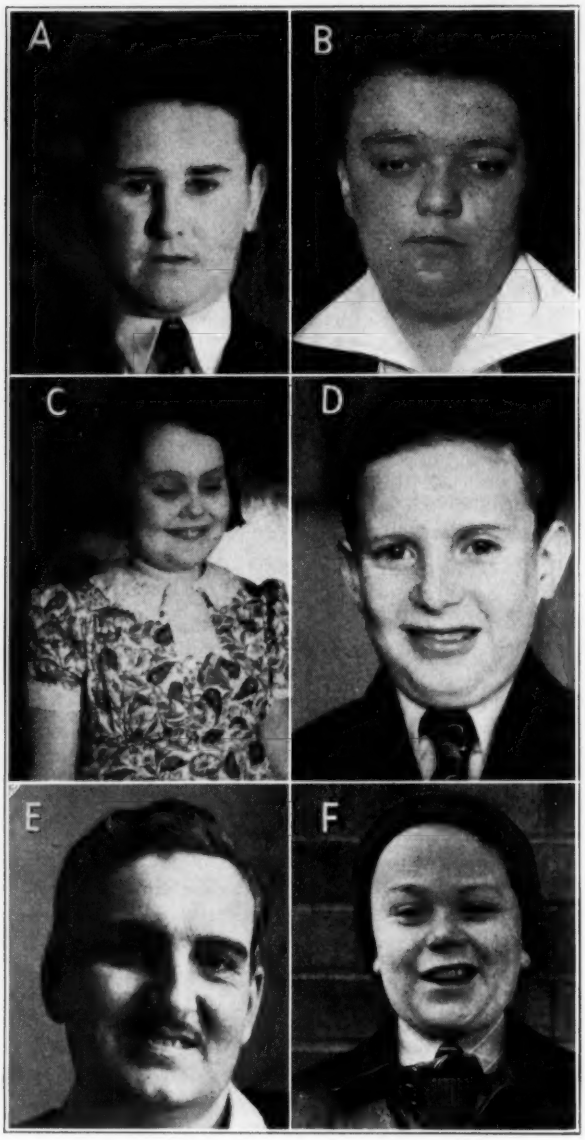

Figure 4

(See legend on opposite page)

Within four months after evacuation of the craniopharyngioma by the conventional method signs of intracranial pressure had returned, and before a full year had elapsed this pressure was so great as to threaten acutely the patient's life.

Although four years have passed since intraventricular drainage was established, not a single symptom or sign has occurred to suggest recurrence of intracranial hypertension. It appears, therefore, that the opening made between cyst and ventricle has remained open and functioning. It is regrettable that this child did not receive the radical type of drainage until a year after she had become completely blind.

From a technical standpoint the operative procedure in this case presents a slight variation from any described in case 2, in that, since the dome of the cyst presented through a widely dilated foramen of Monro, it was unnecessary to make an opening in the floor of the lateral ventricle in order to reach the cyst. The fundamental principle of treatment, however, is exactly the same in this case as in case 2, viz., the drainage of a craniobuccal cyst into the ventricular system.

CASE 4.—S. W., a boy 10 years old, was admitted to the surgical service of the Neurological Institute on April 5, 1937, with complaints of headache and

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EXPLANATION OF FIGURE 4

Fig. 4.—*A* (case 1): At the time this photograph was taken, six years after operation, this young man was regularly employed as a filing clerk.

B (case 2): This boy had had three unsuccessful operations for relief of acute intracranial tension caused by a large craniopharyngioma (fig. 3 *A* and *B*) before intraventricular drainage was at last established. Since then, for over four years, he has remained entirely free of all symptoms and signs of increased intracranial pressure.

C (case 3): This little girl had recurrent symptoms four months after a large craniobuccal cyst had been drained by the conventional method. At a second operation for relief of acute intracranial pressure, the cyst was drained into the ventricular system. This photograph shows the patient as she appears today, four years after her second operation.

D (case 4): Fifteen months after conventional evacuation of a craniobuccal cyst (fig. 3 *C* and *D*) reoperation was urgently necessary. At this time intraventricular drainage was successfully established. The patient has since been symptom free, for two and a half years.

E (case 6): This photograph shows the patient two years after intraventricular drainage. Pneumoencephalograms taken at this time showed marked shrinkage of the original cyst, as well as reduction in size of the previously dilated ventricles (fig. 6).

F (case 7): Five weeks after drainage by the conventional method symptoms returned, because of refilling of the cyst. Since a second operation, when intraventricular drainage was established, nearly two years have elapsed. The patient is now attending public school.

vomiting for approximately two years. He was extremely small for his age, almost a dwarf. Examination revealed reduction of visual acuity, pallor of the optic nerve heads, bitemporal hemianopia, enlargement of the sella turcica with atrophy of the clinoid processes and suprasellar calcification, findings which led to a diagnosis of craniopharyngioma.

Ventriculograms revealed a large suprasellar lesion, extending more to the left of the midline than to the right (fig. 3 *C, D*).

Operation.—On April 23 a left transfrontal craniotomy was performed. After release of pressure by means of a ventricular tap, the dura was opened freely, a transcortical incision was made and the frontal horn of the left lateral ventricle was entered. In the floor of the ventricle, located medially and anterior to the foramen of Monro, was plainly visible a dome-shaped elevation about 3 cm. across, arising perhaps 1 or 1.5 cm. above the general level of the floor of the ventricle. Using a blunt dissector, a circular opening was made through the floor of the ventricle overlying this dome-shaped mass. The floor of the ventricle at this point was rather thin, measuring about 3 mm. in thickness. The operator then came down directly on the top of a large, smooth-walled cyst. After this was carefully cleaned off, a window approximately 2 cm. in diameter was cut in the roof of the cyst. A large amount of chocolate-colored fluid was evacuated with the aid of a sucker, care being taken during the procedure to prevent dissemination of the contents of the cyst into the ventricular system in general. After the cyst had been thoroughly irrigated it was seen that its inner surface was smooth and glistening. Practically the entire bulk of the craniopharyngioma was made up of this single cyst. It was possible, in fact, to advance the tip of the forceps under direct vision far down into the sella turcica. After this, the purpose of the operation having been completed, closure was carried out in layers, without drainage.

The immediate postoperative course was smooth and uncomplicated. There was complete disappearance of all signs of general intracranial pressure, and a promising improvement in the visual fields was already apparent at the time of his discharge, on May 27.

Second Admission.—The patient was readmitted to the Neurological Institute on July 14, 1938, because of persistent, recurring bouts of headache, nausea and vomiting, which were growing progressively worse. Recently vision had become impaired and bitemporal hemianopia had developed.

Encephalograms showed distention of the original suprasellar cyst, with further bulging of its dome into the floor of the left lateral ventricle.

Second Operation.—On July 20 the original left frontal bone flap was reelevated and the left lateral ventricle entered through the scar of the previous transfrontal incision. In the floor of the frontal horn of the ventricle there was a sligthly bluish area, about 1.5 cm. in diameter; when this was examined more closely it proved to be the dome of a suprasellar cyst, showing through a tenuous membrane of brain tissue. The opening originally made in the cyst could not be definitely identified. A new opening was, therefore, made through the dome of the cyst, and this was enlarged until it was approximately 2 cm. in diameter. A large amount of thick, syrupy fluid, having a dark brownish color and a tenacious mucoid consistency, was evacuated from the cyst with the sucker. This fluid was not measured, but the amount was estimated to be about 30 to 40 cc.

The cyst was then thoroughly flushed out with physiologic solution of sodium chloride, after which its character and extent could be studied. Its greatest measurable diameter was 5 cm. The cavity of the cyst extended downward to the floor of the skull, and in the lower portion of the cyst wall there was a

small opening, which appeared to enter the pituitary fossa. The inner surface of the cyst was smooth and white. No vestige of the previously created defect in the wall could be seen. Running over the top of the cyst, close to the margin of the new window just cut into it, was a large artery, apparently rising from the anterior cerebral artery.

After the operator had established communication between the floor of the ventricle and the dome of the cyst, he withdrew from work on the ventricle. He then gently elevated the frontal lobe from the floor of the frontal fossa and inspected the region of the optic chiasm from the outside. The wall of the craniopharyngioma was plainly visible beneath the chiasm and between the optic nerves. It was thin and flexible. No evidence of solid, cellular tumor tissue was anywhere to be seen. No opening was made through the thin wall of the cyst at this point, for fear that this might interfere with the establishment of permanent drainage from the cavity of the cyst into the ventricular system. Closure was made in the usual fashion, the dura, galea and skin being tightly approximated without drainage.

The patient withstood this procedure extremely well. All signs of generalized intracranial pressure were completely relieved. He was discharged on August 4.

Approximately two and a half years have now elapsed since his last operation. During this time there has been no recurrence of symptoms or signs of intracranial pressure. The patient in general feels fairly well. Visual acuity and visual fields in the left eye are essentially normal. While vision in the right eye was badly compromised before operation, further unfavorable progress seems to have been arrested (fig. 4 *D*). The patient has since completed successfully the eighth grade of the public school.

After one unsuccessful attempt at intraventricular drainage, a successful result was apparently obtained at the second operation. The patient has now been free from symptoms of general intracranial pressure and of local advancing pressure for approximately two and a half years.

This case afforded opportunity to investigate, at first hand, the exact anatomic position and significance of the flecks of calcification seen in and above the sella turcica in the roentgenograms. When symptoms recurred after the first intraventricular drainage of the cyst, the operator feared that he had left solid tumor tissue behind in the vicinity of the sella turcica and that this solid portion was directly compressing the optic chiasm and optic nerves. Reexamination of the roentgenograms at the time of the patient's second admission showed slight increase in the number and density of the calcified flecks situated above the sella, and this finding increased the surgeon's apprehension that the recurrence of symptoms was due to the growth of a solid cellular element. This fear, however, was shown at the second operation to be unfounded.

Finally, this case demonstrated clearly that intraventricular exploration may very simply be combined with an extracerebral, subfrontal exposure of the region of the chiasm if conditions warrant it. The one approach to the lesion in no sense precludes the other; the two may be effectively combined in certain cases.

CASE 5.—T. de C., an Italian girl aged 11 years, was admitted to the Neurological Institute on March 20, 1939, with headache, vomiting and blurring of vision, which had developed over a period of seven months.

Examination revealed a very obese child, with protuberant abdomen, large breasts, absence of pubic hair and long, thin fingers. The margins of the optic disks were blurred and the disks themselves somewhat injected. Vision in the right eye was 20/70, with complete temporal hemianopia. Vision in the left eye was 3/200, and the fields were impossible to chart. The results of neurologic examination were otherwise negative.

Roentgenograms of the skull revealed a considerable amount of calcification in and above the sella turcica and extending a considerable distance to each side of the midline. The roentgenologist interpreted this finding as indicating a craniopharyngioma.

A ventriculogram showed the lateral ventricles to be enlarged and displaced to the right of the midline. A tumor extended posteriorly and to the left, encroaching upward on the floor of the left lateral ventricle and producing a large filling defect in the atrium of the ventricle (fig. 3 *E* and *F*).

Operation.—On March 29 a left parietal osteoplastic craniotomy was performed. Intraventricular tension was relieved by tapping the ventricle. A transcortical incision about 2.5 cm. in length was then made in the region of the angular gyrus, and the ventricle was entered. In the atrium of the ventricle, coming from an anterior position and projecting backward, was seen the smooth, rounded end of a large cystic tumor. This cyst was carefully walled off from the rest of the ventricle, and a circular window, approximately 2 cm. in diameter, was made through the wall of the cyst at that portion where it lay free in the ventricular cavity. As the opening was made there escaped under considerable pressure a large amount of thick, yellow fluid, containing small refractile particles. This was removed with the sucker as quickly as possible to prevent its dissemination in the ventricle, with the result that actual measurement of the amount was not obtained, but it was estimated that about 50 cc. was removed from the cyst.

After the cavity of the cyst was thoroughly washed out with physiologic solution of sodium chloride it was thoroughly inspected. The wall was about 3 mm. in thickness. Its inner surface on the whole was smooth and glistening, with here and there small calcific deposits projecting slightly from the wall into the cavity. These were apparently covered with a thin layer of epithelium. The operator was able to see and to pass a probe anteriorly and inferiorly into a region which he thought to be near the sella turcica. Nothing was seen at this inspection which resembled either a solid, cellular mass or secondary, multiloculated cysts.

Unfortunately, the wall of the cyst failed to collapse after the release of its fluid contents. This was due to its tough, unyielding nature. Efforts to collapse it forcibly were unsuccessful and actually caused slight bleeding from inaccessible regions between the cyst wall and the adjacent portion of the brain; the hemorrhage was controlled only after some little difficulty, so that the operator felt it unwise to pursue the tactic further.

The operation was, therefore, terminated at this stage and a tight closure effected in the usual manner, without drainage. Microscopic examination of the tissue of that portion of the wall which was removed was reported by Dr. Abner Wolf as being adamantinoma of craniobuccal origin. In estimating the value of the procedure at the conclusion of the operation, the operator felt that while he had produced an effective, and probably permanent, drainage of the craniopharyn-

gioma into the lateral ventricle, he had not actually relieved the compression and closure of the foramens of Monro, owing to the unyielding nature of the wall of the cyst. For this reason, therefore, he held a guarded prognosis regarding permanent improvement.

The immediate postoperative recovery was rapid and uneventful. There was no aphasia after the operation, but the patient complained of a constant, buzzing noise referred to the left ear. The patient was discharged on April 26, about four weeks after her operation, at which time there was no appreciable change in her visual functions, but complete relief from symptoms of general intracranial pressure.

Second Admission.—The patient was readmitted to the surgical service of the Neurological Institute on Aug. 3, 1939. Her parents stated that she had continued to have poor vision ever since her last hospitalization, but that this had been stationary and that the headaches had not been troublesome until about the middle of July 1939, three weeks before her current admission. At this time the headaches became abruptly worse and again were associated with nausea and vomiting. Simultaneously with these symptoms the parents noticed that the bone flap had become more bulging and tense.

The patient walked into the hospital but was obviously ill. The bone flap was elevated and tense. Quantitative visual tests showed no essential changes since her last hospitalization. Examination of the optic fundi at this time revealed marked congestion and tortuosity of the retinal veins, which had not been present previously, indications of generalized intracranial pressure.

Second Operation.—On August 10 the old left temporal bone flap was reelevated to make certain that the communication between the cavity of the cyst and the ventricle was functioning properly.

The ventricle was easily entered along the tract of the previous transcortical incision and the craniopharyngioma brought immediately into view. The opening which had been made through its wall at the first operation was still widely open and measured 1.5 cm. in diameter. The edges of the opening appeared to be epithelialized and smooth, without any evidence of exposed granulation tissue. From all appearances, the healing processes at the site of the opening had been completed and the status of the opening had been permanently fixed. A photograph taken at this time shows this clearly (fig. 5). There was free communication between the cavity of the ventricle and the cavity of the cyst, and the latter was filled with clear, colorless cerebrospinal fluid. The appearance of the inside of the cyst was essentially the same as that described at the previous operation.

It was obvious, therefore, that the progressive downhill course was not due to distention of the craniobuccal cyst by secretions within it, but that symptoms must be due to pressure against the foramens of Monro and the floor of the third ventricle by the rigid unyielding wall of the cyst, which, in turn, produced a high grade of obstructive hydrocephalus. For this reason an attempt was again made at this time forcibly to collapse the wall of the cyst, but again the threat of uncontrollable bleeding from inaccessible regions behind the cyst terminated this attempt. The operation was, therefore, concluded at this point. Closure was effected in the usual manner, without drainage.

It was felt that nothing had been accomplished for the relief of the child's symptoms in this operation.

Third Operation.—On August 28 a third attack was made on the craniopharyngioma. At this operation a right transfrontal flap was turned up, and the anterior horn of the right lateral ventricle was entered through a transcortical incision. The right foramen of Monro was reduced to a curved slit. Through

this, by slight retraction, could be seen the top of the dome of the suprasellar cyst. This was punctured with the tip of the forceps, with the escape of some fluid, of which part looked like heavy crankcase oil and other parts resembled mayonnaise, but both fluids had the peculiar refractive appearance of suspensions of cholesterol or lecithin crystals.

The pillars of the fornix were then divided, and the inferior mesial corner of the lateral ventricle behind the foramen of Monro was incised from the edge of the foramen backward for a distance of about 1½ inches (3.8 cm.), thus bringing into the field the entire top of the third ventricle. This ventricle was found to be entirely filled with the craniopharyngioma, which proved to be in large part solid tumor punctuated with small cystic loculations. This tumor was then

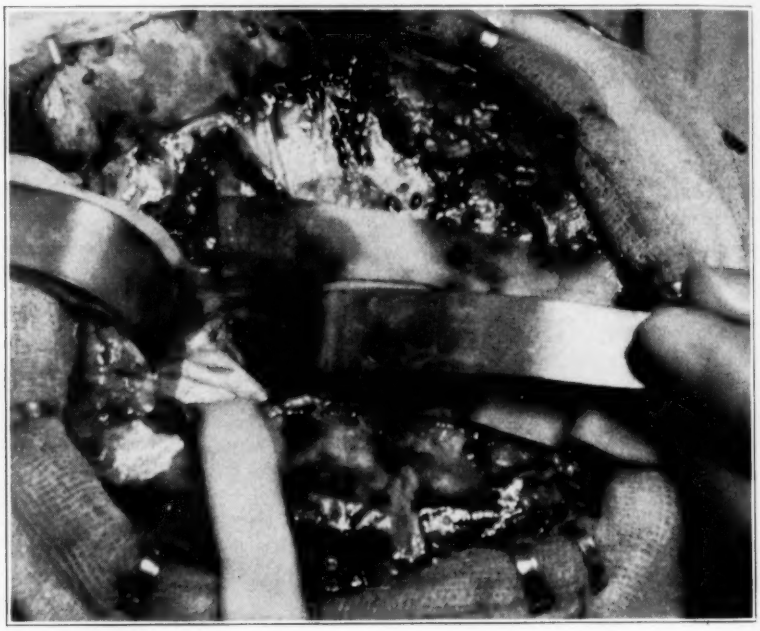

Fig. 5.—This photograph was taken during the second operation in case 5 (fig. 3, *E* and *F*). The atrium of the left lateral ventricle has been entered through a small linear transdural and transcortical incision, which is being held open by retractors. In the floor of the ventricle may be seen a circular opening approximately 1.5 to 2 cm. in diameter, which leads from the ventricle directly into a large craniobuccal cyst. This opening had been made at a previous operation three months before. Its edges are completely epithelized, and all tendency for the opening to close has ceased.

removed piecemeal, after separating it carefully from the adjacent thalamus on each side. Precautions were taken to prevent blood from draining backward into the aqueduct of Sylvius. Finally, the entire contents of the third ventricle were removed, leaving smooth, and apparently untraumatized, walls on each side. The opening of the aqueduct of Sylvius was visible posteriorly, and the left foramen of Monro was seen to the left. The field was quite dry.

At the end of this procedure the patient's general condition and vital signs appeared good. There was no hyperthermia or evidence of shock. The whole procedure had been carried out with a minimal loss of blood, which was more than replaced by transfusions. For the first two hours after the operation his general condition appeared to be excellent. There then developed a sudden and alarming fall in blood pressure, attended by an increase in the pulse rate. The reaction appeared to be a primary vasomotor collapse. This condition became progressively worse in spite of all efforts to correct it, and the patient died in shock approximately twenty-four hours after the operation.

In spite of the fatal outcome, this case is instructive from several standpoints. First, it illustrates in a dramatic fashion the extent to which a craniopharyngioma may "wander" from its original intrasellar or suprasellar position, and it emphasizes the value of ventriculography before operation.

Second, this case illustrates the polymorphous nature of some of the craniopharyngiomas. In this instance, the tumor consisted of both a large, smooth-walled cystic portion and a solid, cellular or multilocular portion. The anatomic structure of this tumor should be compared with the anatomic structure of the tumor found in case 4, in which careful inspection excluded the existence of any solid cellular portion. The thick, unyielding wall of the cystic portion of this tumor offers a good explanation of why many patients are not relieved of their symptoms, even after complete evacuation of a large, single craniobuccal cyst, the reason being that owing to the rigidity of the wall the cyst retains its original size and shape even after drainage of its liquid contents.

Third, this case illustrates the necessity of having different approaches to, and different methods of surgical attack on, craniopharyngiomas. It is obvious that the conventional subfrontal and parachiasmatic exposure would have been completely futile in this case. Such an approach would not have permitted the removal of any significant portion of the solid tumor, certainly not enough to decompress the foramens of Monro and the third ventricle sufficiently to relieve the obstructive hydrocephalus. Nor would it in this case have permitted drainage of the large cyst lying above and beyond the solid portion of the tumor. The only possible hope of relieving the obstructive hydrocephalus in this case lay in free exposure of the foramens of Monro and the third ventricle and direct attack on the tumor in this region.

Finally, this case afforded a good opportunity to demonstrate the persistence of one of the openings between a craniobuccal cyst and a cerebral ventricle some months after it had been made.

CASE 6.—W. B., a man aged 30, was a private patient of Dr. Byron Stookey. In operating on him, Dr. Stookey employed the technic here described and has given me permission to report his case with my own.

First Admission.—This patient, a 30 year old commercial aviator, was admitted to the private pavilion of the Neurological Institute on March 21, 1938, com-

plaining of rapid gain of weight, progressive drowsiness, loss of memory, reduction in sexual libido and failing vision, all of which had developed during the two years before admission. Recently there had been marked acceleration in the severity of these symptoms.

Study revealed the presence of a large craniopharyngioma (fig. 6 *A*).

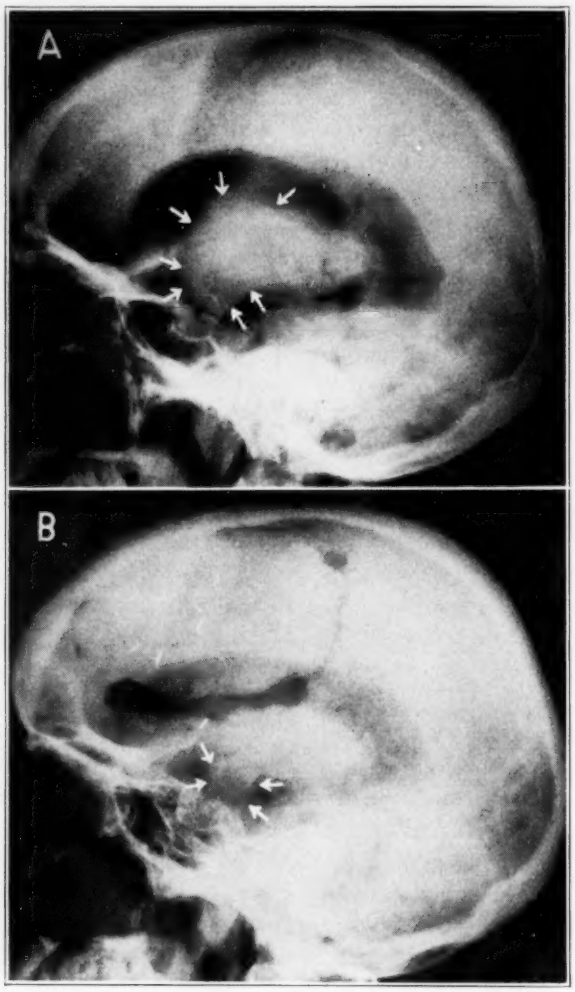

Fig. 6.—Pneumoencephalograms in case 6.

A, taken before operation, shows a large craniobuccal cyst above the sella far enough to push up the floor of the lateral ventricles (see arrows).

B, taken two years after the craniobuccal cyst had been drained into the lateral ventricle (fig. 4 *E*), shows in only a small nubbin of tumor immediately above the sella turcica. Note that the ventricles appear to be slightly smaller than they were before operation.

First Operation.—On March 28 a right frontal craniotomy was performed and the frontal horn of the right lateral ventricle was entered through a transcortical incision in the posterior part of the middle frontal convolution. There was a bulge in the floor of the frontal horn of the ventricle near the medial wall, and palpation indicated that this was due to pressure exerted by an underlying cyst. An opening was forced through this bulge in the floor of the ventricle with the tip of the forceps. A large cyst was entered, from which there escaped a considerable amount of yellowish fluid, containing a fine suspension of refractile bodies. This was removed with a sucker as fast as it escaped, in order to prevent its dissemination in the ventricle. The opening of the cyst was then enlarged until it approximated 3 cm. in diameter. By means of the sucker, the entire contents of the cyst were then evacuated. A portion of the wall of the cyst was examined by Dr. Abner Wolf and reported to be adamantinoma of bucconeural origin. The inside of the cyst was thoroughly irrigated and filled with physiologic solution of sodium chloride. After this the wound was closed in the usual manner, without drainage.

The immediate postoperative course was smooth and uncomplicated; the patient was discharged from the hospital on April 22.

Second Admission.—The patient was readmitted to the Neurological Institute on Nov. 14, 1940, with essentially the same symptoms that he had had at the time of his first admission. The examination showed a well healed craniotomy wound, which was not bulging. Vision in the left eye was 20/200, and there was a partial lower quadrant bitemporal field defect. The optic nerve heads appeared to be normal, and there was no evidence of vascular congestion. The general neurologic examination failed to reveal anything else of significance. A marked reduction in his intellectual functions, however, had taken place since his last admission to the hospital. At times he was euphoric and completely disoriented and was confused in his understanding and judgment (fig. 4*E*).

Pneumoencephalograms were made at this time (fig. 6*B*) and were reported on by Dr. Cornelius Dyke as follows: "These show that the lateral and third ventricles are definitely smaller than when the last encephalogram was made in March 1938, two and a half years ago. There is a small concave defect in the cisterna interpeduncularis, indicating the presence of a small mass just above the sella turcica, and at this point there are a few small flecks of calcification; but in comparing the present encephalogram with the one made in March 1938 it is strikingly clear that the mass is considerably smaller in the more recent roentgenograms. In March 1938 the mass extended above the sella turcica for a distance of over 4 cm. and the anteroposterior diameter of the mass measured 4 cm.; at present it measures barely 2 cm. Moreover, there is no evidence of reformation of the original cyst or of encroachment on the region of the foramen of Monro in the present plates, as there was in the plates taken two years ago prior to operation. It is therefore, quite evident that there has been a marked decrease in the size of the craniopharyngioma since the operation in March 1938."

It was felt that the patient's chief presenting symptom, intellectual deterioration, could not be explained on the basis of a small residual nubbin of tumor tissue in the vicinity of the chiasm and that, in view of the meager signs of focal pressure at the chiasm and in the absence of any signs of generalized intracranial pressure, there were inadequate grounds for surgical reexploration. The patient was accordingly discharged from the hospital without further treatment. The cause of his progressive mental deterioration was not discovered.

This case is interesting because it supplies direct roentgenographic evidence of (1) marked shrinkage of the craniobuccal cyst two years after intraventricular drainage had been established and (2) reduction in size of the ventricular system, which had been dilated, after establishment of the intraventricular drainage. This could have occurred only if the obstruction to the circulation of the spinal fluid produced by the craniopharyngioma before the operation had been effectively removed by the operation and had remained so.

Case 8.—W. H., a boy 11 years old, was admitted to the surgical ward of the Neurological Institute as a service case, where he was assigned to the care of Dr. Fritz Cramer. At a second operation, Dr. Cramer employed the method of intraventricular drainage which I had already described to the neurosurgical staff, and he has permitted me to include this case in reporting my method of operation.

First Admission.—The patient was first admitted to the hospital on Aug. 24, 1938, complaining of frontal headaches and visual disturbances of five months' duration. Examination revealed marked reduction in visual acuity, bitemporal hemianopia and papilledema, with an elevation of several diopters. A clinical diagnosis of craniopharyngioma was made. Ventriculograms revealed slightly dilated ventricles and evidence of a tumor in the suprasellar region, pushing upward and compressing the third ventricle.

First Operation.—On September 2 a right frontal craniotomy was performed and the chiasm was exposed by a subfrontal approach. A thin membrane could then be seen bulging above the chiasm and compressing the chiasm and the right optic nerve. This was incised, with evacuation of a large, but unmeasured, amount of greenish yellow, rather thick fluid, containing numerous refractile particles. It was estimated by the operator that about 75 cc. of this fluid was removed. After this closure was effected in the usual manner.

The patient ran a smooth postoperative course, with complete relief of symptoms of generalized intracranial pressure, including the disappearance of papilledema. Visual acuity, however, continued to be poor (5/200 in both eyes). He was discharged on September 17, the fifteenth postoperative day.

Second Admission.—The patient was readmitted to the Neurological Institute on Jan. 28, 1939, with the same symptoms which he had previously had. Examination on this occasion revealed pallor of the optic nerves, bitemporal hemianopia and visual acuity of both eyes which permitted the counting of fingers at a distance of 5 feet (152 cm.). It was the impression that the craniopharyngioma had refilled, and reoperation was undertaken on this assumption.

Second Operation.—On February 2 the right frontal osteoplastic flap was reelevated and the frontal horn of the right lateral ventricle was entered through a small transcortical incision. At once it was seen that the foramen of Monro was occluded by a moderately firm, bluish membrane. When this was punctured, the cyst proved to contain a deep yellow, clear fluid. On incision of the wall of the foramen of Monro and extension of the incision along the floor of the lateral ventricle, another cystic mass became apparent. This contained fluid similar to that which was obtained when the membrane over the foramen was tapped. It is noteworthy that this fluid did not contain cholesterol crystals but was clear and yellow and coagulated quickly. The wall of this cyst was opened widely, and the cyst, when emptied, was found to communicate freely with the lateral ventricle. It was the impression of the operator that the cyst had invagi-

nated the anterior lateral wall of the third ventricle into the foramen of Monro, for when the cyst had been emptied the foramen of Monro was clear of obstruction. No solid tumor could be seen. At the completion of this inspection, closure was made in the usual manner.

The microscopic diagnosis made by Dr. Abner Wolf of tissue removed from the wall of the cyst was adamantinoma of craniobuccal origin.

The patient withstood the procedure well and made an uneventful recovery. All papilledema subsided while the patient was in the ward, and the bone flap remained flat. The patient was discharged on February 21, the eighteenth postoperative day.

The patient was last seen on Feb. 8, 1941, just two years after his last operation. Visual acuity was then about 5/200 in each eye, and hemianopic field defects still persisted. However, this condition has remained stationary since his last operation and is largely the result of the marked primary and secondary atrophy present at the time of his operation. Furthermore, during this interval there has been no return whatever of the signs of intracranial pressure from which he suffered acutely prior to his operation. The boy is attending public school, where he is able to make satisfactory progress in classes designed for conservation of sight. He has grown slightly and in general appears to be in good health (fig. 4*F*).

Six weeks after evacuation of a large craniobuccal cyst, by the conventional operation, this patient began to have return of the symptoms of intracranial pressure, and four months after the evacuation of the cyst he was suffering so severely that a second operation was necessary. In contrast to this unsatisfactory result, the patient has now lived nearly two years after intraventricular drainage by the technic here described, without any evidence whatever of recurrent pressure.

The cyst in this instance was first identified through the foramen of Monro, as it pushed up the thin floor of the third ventricle, and it was easily opened at this point. In this respect it resembled the cyst in case 3, previously described, which I treated satisfactorily in the same manner. The principle involved in this procedure, however, is common to all of the cases here reported, viz., drainage of the craniobuccal cyst into the ventricular system. Naturally, this should be done where it can be done most easily.

COMMENT

Selection of Cases: Limitations of the Method.—The new method of treatment herewith described can be utilized only in selected cases. The factors determining the selection of the cases suitable for this method of treatment are, primarily, (1) the size of the craniopharyngioma and (2) the nature of the tumor, that is, whether it is cystic or solid.

1. The *size* of the lesion is of paramount importance in the selection of cases for this operative procedure, for unless the lesion is large enough to push up and thin out the floor of the lateral ventricles no attempt should be made to deal with it in this fashion.

The character of the patient's symptoms and signs will often give a valuable clue to the probable size of the cyst. If these indicate only pressure on the optic nerves and the chiasm, then the chances are that the lesion is small; on the other hand, if the patient, in addition to signs of local pressure at the chiasm, has signs of generalized intracranial pressure, including headache and vomiting, then one may well assume that the cyst has reached such size as to occlude the foramens of Monro or the third ventricle itself. If the wall of the cyst contains calcium, its position and extent may be clearly shown by ordinary roentgen examination.

Ventriculography, however, affords the only certain way of determining the exact size and position of the cyst and its relation to the floor of the lateral ventricle. For this reason I feel that ventriculograms should be made in practically all cases of craniopharyngioma as an important means of determining the proper operative procedure.

2. The *character* of the individual craniopharyngioma is also of great importance in determining the applicability and the usefulness of this procedure. The method, obviously, is most useful in the treatment of a large, single, comparatively thin-walled cyst and is less useful in the management of a solid, cellular craniopharyngioma. Unfortunately, it is not possible before operation to determine with certainty whether the craniopharyngioma is cystic or solid.

In general, the small craniopharyngioma which produces signs only by pressure on the optic nerves, and which does not obstruct the lateral ventricles, should in all instances be operated on by the conventional subfrontal approach, since that is the only route by which it can be reached. Moreover, in such a case the direct approach to the chiasm assures relief from pressure at the only point then urgently demanding relief, viz., the optic nerves and chiasm.

On the other hand, a craniopharyngioma which is so large that it has pushed up the floor of the lateral ventricles, obstructed the foramen of Monro and produced hydrocephalus may be properly explored by this new method. If the lesion actually is cystic, then intraventricular drainage, in my opinion, is the method of choice, whereas if the lesion is solid effective attack on that portion of the tumor obstructing the ventricular system and actually constituting the chief threat to life can be made only by a transventricular approach to that portion of the tumor compressing or blocking the foramens of Monro. In such a case the amount of solid tissue which it would be possible to remove by the usual surgical exposure of the optic chiasm would be totally ineffectual in decompressing these foramens and in relieving the patient's hydrocephalus.

Finally, it should be pointed out that a negative transventricular exploration does not at all preclude an immediate subfrontal exploration of the region of the chiasm at the same operative session. With the dilated ventricle which a patient with such a tumor would have, elevation

of the frontal lobe sufficient to expose the chiasm is a relatively simple matter. This was done in case 4, at the second operation.

In case there is doubt into which of these two categories any tumor properly falls, the lesion should first be exposed and treated by means of the older, extracerebral, subfrontal approach, but even when this is intended the opening in the bone should be large enough to give adequate exposure for a transcortical-transventricular approach to the cyst, should that procedure subsequently seem indicated.

Results of Treatment by the New Method.—A statistical comparison between the results obtained by the conventional methods of treating craniopharyngiomas and the method I have described in this paper is not justified on the basis of 7 cases. However, from the cases studied and here presented, it seems clear that the establishment of a well functioning opening between the cystic portion of a craniopharyngioma and one of the cerebral ventricles is, as a matter of fact, possible, and, once affected, would seem to afford a more nearly permanent drainage for the cyst than the older method.

SUMMARY

The conventional treatment of craniobuccal cysts has proved unsatisfactory in the past, for the reason that it did not provide for permanent drainage of the secretions which continue to be elaborated from the inner lining of these cysts during the lifetime of the patient. Because of this, these cysts tended to refill, redistend and reproduce symptoms of local pressure and of obstruction to the cerebrospinal fluid circulation, in spite of completely satisfactory evacuation at the time of operation.

A new method of treating craniobuccal cysts, characterized as *intraventricular drainage,* is here described. The basic principle consists of establishing a communication between the dome of the cyst and the floor of the lateral ventricle. There is reason to hope that such an opening, if adequately made, will remain patent, thereby allowing permanent drainage of the secretions coming from the lining of the cyst into the cerebrospinal fluid circulation and their absorption with this fluid.

Seven cases illustrating this new method are reported. Some of the experiences have been encouraging; some have been discouraging, but all have been enlightening. The cases are reported in detail. In selected instances the method offers promise of better results than operation by the older conventional method.

ROENTGENOLOGIC CHANGES IN THE BONES IN CASES OF PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

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BROOKLYN

Ever since Cruveilhier reported the necropsy observations in a case of muscular dystrophy the common concept has been that the muscular system is primarily affected in this disease. Friedreich and Erb delineated the various clinical patterns of the condition and stressed the muscular involvement. There has been discussion whether or not the central nervous system may also be involved. Alterations in the carbohydrate and creatinine metabolism have been demonstrated recently.[1] Occasional necropsy reports have disclosed pathologic changes in various endocrine glands, but no causal relation has been established.[2]

From time to time brief mention of involvement of bone has appeared, suggesting that myopathies may represent a process of more generalized nature than one involving only the muscles. Since both muscle and bone are of mesodermal origin, it is conceivable that the disease might be due to some alteration in the growth potentialities of the mesoderm.

It appeared to be of interest to determine how often skeletal changes might be demonstrated in patients with muscular dystrophy. We had the opportunity of studying 7 patients confined to an institution for chronic diseases. The diagnosis of progressive muscular dystrophy was made by one of us (J. L. A.) and confirmed by other neurologists.

REPORT OF CASES

CASE 1.—A. S., a 16 year old boy, was born by normal spontaneous delivery. A family history of muscular disorders could not be elicited. He was considered of average health until the age of 7 years. His first complaints were weakness of the lower extremities and frequent falling. The weakness progressed rapidly

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1. Magee, M. C.: Creatinine Metabolism in Progressive Muscular Dystrophy, Am. J. Dis. Child. **43**:18 (Jan.) 1932.

2. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in the Myopathies, J. A. M. A. **101**:1047 (Sept. 30) 1933.

and soon involved his upper extremities. When admitted to the hospital in 1935 he presented a typical picture of pseudohypertrophic muscular dystrophy.

The patient was moderately obese. There was marked weakness of the musculature of the thorax and upper extremities with no visible evidence of structural change. He was unable to raise his hands to his mouth. The scapulas were winged. In order to raise himself he had to "climb on himself," a rather typical observation in this condition. His thighs were heavy, and his calf muscles were prominent. He retained slight motion of his lower extremities. There were bilateral foot drop and increased lumbar lordosis.

Roentgenographic examination of the shoulders showed that both scapulas were small. There was definite disproportion between the large humeral heads and the small, shallow glenoid fossae. The humeral epiphyses were ununited. The humeral shafts were slender, and there was slight widening of the medullary canal. The cortex of the bone was of normal density, and no increase in trabecular markings was present. The bones of the forearms were also slender but of normal length. The diameters of the radius and the ulna were no greater than those of the metacarpal bones. The epiphyses of the hands were open, and their bony structure was not remarkable.

The lumbar position of the spine was scoliotic, with the convexity toward the left. The vertebral bodies were intact. The pelvis was small, and the iliac bones were flared. The ischial spines were unusually prominent. The femoral necks showed marked coxa valga, but were not thin. The femoral shafts, however, were of almost pipestem configuration. Their medullary canals appeared to be widened. The cortex of the bone was of normal density. The feet were small, and their bony structures appeared thin and delicate.

CASE 2.—H. G., a 15 year old boy, did not walk until he was 2 years old. His gait then was unsteady, and he waddled. Gradual improvement occurred, so that by the time he was 9 years old he could walk several blocks. He then began to tire easily and gradually lost the ability either to walk or to sit up. Two maternal uncles were known to have similar conditions.

The patient was a thin lad of average height. He had fairly good movement of the muscles of the neck and slight mobility of the shoulders and elbows. Finger movement was fairly good, and he could move his lower extremities and toes slightly. The range of motion was insufficient to permit him to attend to his needs, and he was confined to a wheel chair. His upper extremities and femurs were thin; his calf muscles were heavy.

Roentgenographic examination of the shoulders showed very small scapulas, with disproportionately large humeral heads and small, shallow glenoid fossae. The humeral shafts were slender and the medullary canals slightly widened. The density of the cortex of the bone was normal. The epiphyses of the humeri were united. The chest was normal.

The pelvis was small and asymmetric. The right iliac bone was flared and the left foreshortened. There was marked coxa valga of both hips. The femoral shafts were normal in size and bone density. The knees were permanently flexed. The upper halves of the tibias and fibulas were normal. The skull was normal.

CASE 3.—A. C., a 15 year old boy, had a normal birth. His family history was irrelevant. He sat up when 1 year old and began to walk with a waddling gait at the age of 18 months. At that time he had to "climb on himself" to arise and walked on his toes. He had been confined to a wheel chair since the age of 7 years. When

admitted he presented the picture of pseudohypertrophic muscular dystrophy, with typical enlargement of the calves of the legs. He retained slight use of his hands and less use of his lower extremities. There was bilateral foot drop.

Roentgenographic examination of the shoulders showed small scapulas. The humeral heads were large, and the shafts of the bones were very slender. The cortex of the bone was normal in density, and the medullary canals were slightly widened. The forearms showed similar alterations in bone structure. Slight anterior bowing of the tibias was present, and there was thinning of the shafts of both the tibias and the fibulas.

The spine was normal. The pelvis was small and showed flaring of the iliac bones. Both hips presented a thin acetabular rim and coxa valga. The pelvis was foreshortened because of the marked lumbar lordosis. The ischial spines were very prominent. The upper portions of the femoral shafts were thin but showed normal architectural patterns. The femoral necks were larger in diameter than the femoral shafts.

Case 4.—N. B., a 15 year old boy, had a normal spontaneous birth. He was well until the age of 7 years. At that time weakness of his lower extremities appeared, and he slowly lost the ability to walk. He then began to lose strength in his upper extremities. At the time of admission there was atrophy of the axioappendicular muscle groups. Motion at the shoulders was slight and was practically absent at the hips. There were flexion contractures of both knees.

Roentgenographic examination of the shoulders showed the humeral heads to be large as compared with the small shallow glenoid fossae. The scapulas were very small. The humeral shafts were slender and of normal length. Their medullary canals were slightly widened. The cortex of the bone was thin and of normal density. The epiphyses were incompletely united. The tibias and fibulas likewise had very thin shafts, with no other osseous changes.

There was curvature of the lumbar portion of the spine, with the convexity toward the left. The vertebral bodies were intact. The iliac bones of the pelvis were flared, the ischial spines were prominent and there was marked coxa valga of both hips.

Case 5.—E. G., a 27 year old man, was well until he was 8 years old. At that time his family noticed that he walked on his toes. He was able to engage in normal activities until the age of 15 years, when weakness of the upper and lower extremities appeared. He then began to show changes characteristic of progressive muscular dystrophy, with pseudohypertrophy of the calf muscles. Since the age of 16 years he has been confined to a wheel chair.

When admitted he retained fairly good motion of his head and neck. He had slight motion of his shoulders and elbows and slightly better finger motion. There were flexure contractures of the hips and knees and bilateral foot drop.

Roentgenographic examination of the shoulders showed large humeral heads in small, shallow glenoid fossae. The scapulas were small. The humeral shafts were slender, with slightly widened medullary canals. The diameters of the humeri were the same as those of the clavicles. The bones of the forearms were normal in size and structure. The lower extremities showed no alterations in structure. The pelvis was small, with prominent ischial spines and marked coxa valga of both hips.

Case 6.—M. H., a 37 year old man, was normal until the age of 5 years. At that time weakness of his lower extremities sufficient to prevent walking appeared.

After this there was progressive weakness of all extremities, so that the patient had been confined to a wheel chair or bed since the age of 20.

Physical examination showed enlargement of the lower extremities, particularly of the calf muscles. The patient was unable to move his lower extremities and had only slight power in his upper limbs. Bilateral foot drop was present.

Roentgenographic examination showed normal shoulder girdles. The humeri were normal. Both lower extremities showed normal osseous structures. His pelvis was small, and there was marked coxa valga of both hips.

CASE 7.—I. R., a 21 year old man, was normal until the age of 4 years. At that time it was noted that he did not close his eyes when asleep. One year later inability to smile or grimace was noted. At the age of 6 years weakness of his extremities appeared, first in the upper and a year later in the lower extremities. This progressed so that soon the patient could get about only in a wheel chair.

Physical examination revealed that he could shrug his shoulders only slightly. He could not elevate his arms, but was able to flex and extend his forearms one at a time with a jerky motion. This was facilitated when the arm was held. His grip was weak. A wrist drop was present on the right. He retained slight motion in the hips, but could not flex the thighs. He could move both feet slightly. There were bilateral paresis of the facial muscles, atrophy of the muscles of the shoulder girdles and the extensors of the thighs and feet and winging of the scapulas.

The diagnosis was that of the Landouzy-Dejerine type of muscular dystrophy.

Roentgenographic examination of the shoulders showed the scapulas to be very small. The humeral heads were fairly large and could be easily and painlessly disarticulated and reposited under fluoroscopic observation by allowing the patient's arms to hang down. The humeral shafts were very thin, but showed no loss of cortical markings. The hands showed normal osseous structures.

The pelvis was small, and both iliac bones were flared. There was marked coxa valga of both hips.

COMMENT

The association of roentgenographic alterations in the bones with pseudohypertrophic muscular dystrophy has been insufficiently stressed in the past. Reference to such changes has been made casually, and, with a few exceptions, the alterations noted did not appear to be of particular significance to the examiner. Thus, in presenting 2 cases with necropsy observations in 1898, Schultze [3] noted thinning of the long bones in 1 case. He stated that the humerus was thinner than the middle finger of a normal hand and that the medullary cavity was small. Up to that time he had been unable to find more than 2 other references to atrophy of the bones with muscular dystrophy—a case of Friedreich's and one of Legender's. In all these cases there was concentric atrophy of the long bones with no diminution in length. No photographs accompanied the article.

3. Schultze, F., cited by Hurwitz.[9]

Timme,[4] in his extensive work on the myopathies, stated that the bony changes were at times atrophic and at times hypertrophic. He showed roentgenograms of 1 patient (case 24) which indicated the thinness of the ulna and radius and the phalanges.

Tixier and Roederer [5] reported 4 cases of muscular dystrophy in which osseous changes resembling dwarfism and osteomalacia were exhibited. Roentgenograms showed decalcification of the epiphyses and, to a lesser extent, of the diaphyses.[5]

Brock and Kay,[6] in presenting 3 cases, mentioned that in 1 (case 2) there was an area of rarefaction at the proximal end of the second

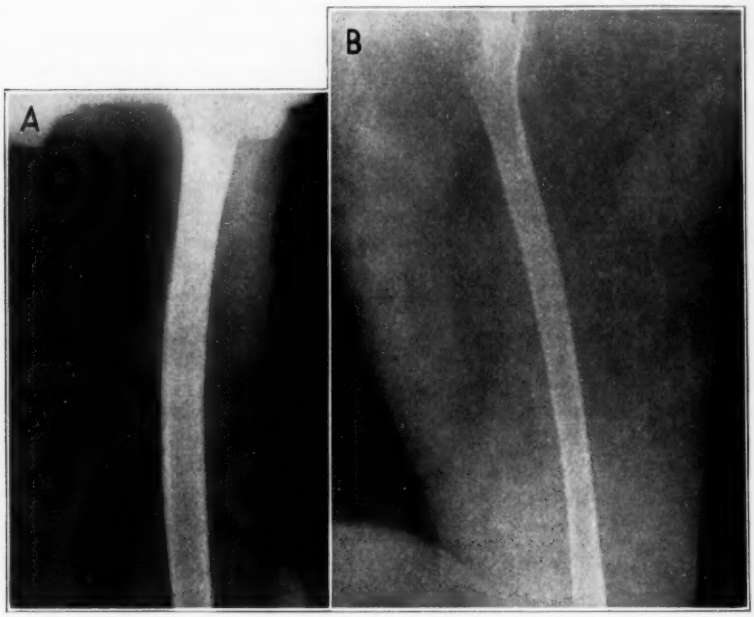

Fig. 1.—*A* (case 2): The density of the cortex of the right femur is normal, the medullary canal widened and the cortex thin. The soft tissues are atrophied. *B* (case 1): The femoral shaft is very slender, in contrast to the obese thigh. The medullary canal is widened and the cortex thin. There is marked coxa valga. The fascial planes usually seen in the soft tissue shadows are not demonstrable.

metacarpal bone bilaterally. No abnormalities were noted in the other 2 cases.

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4. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

5. Tixier, L., and Roederer, C.: Sur un dystrophie ostéomusculaire, Presse méd. **21**:95, 1913.

6. Brock, S., and Kay, W. E.: Study of Unusual Endocrine Disturbances, Their Associated Myopathies, Endocrine Balance and Metabolic Findings, Arch. Int. Med. **27**:1 (Jan.) 1921.

Wright [7] presented 19 cases of progressive muscular dystrophy and stated that roentgenograms showed rarefaction of the bony tissues, but offered no further information. Janney and his co-workers,[8] and later Hurwitz,[9] also described alterations in the long bones and, in occasional instances, in the skull. Hurwitz expressed the belief that these changes were due to disuse but also observed that the bones "appeared as thin as pipe-stems" in 1 instance (case 33).

Aside from these references, we could not find in the available literature further information regarding changes in the bones in pseudohypertrophic muscular dystrophy. Our own series of patients showed interesting features which we feel deserve emphasis.

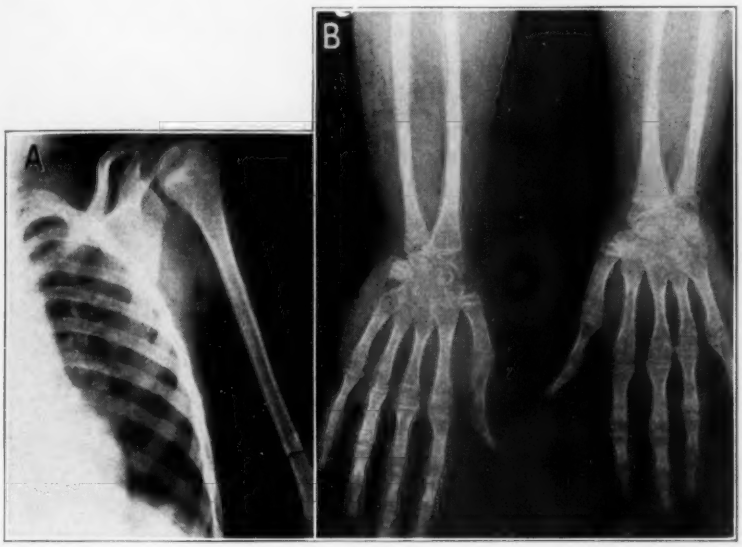

Fig. 2.—*A* (case 4): The left humerus has a large head and slender shaft with normal density of the bone. The cortex is thin and the medullary canal widened. *B* (case 1): The radiuses and ulnas are very slender, approaching the pipestem appearance. Note that the diameters of the distal portions of the long bones are about the same as those of the metacarpal bones.

Alterations in the roentgenographic appearance of the bones were found in the scapulas and long bones of 6 and the pelves of all 7 patients.

7. Wright, C.: Consideration of Progressive Muscular Dystrophy with Pseudohypertrophy from an Endocrine Standpoint, California & West. Med. **23:** 999, 1925.

8. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21:**188 (Feb.) 1918.

9. Hurwitz, S.: Primary Myopathies, Arch. Neurol. & Psychiat. **36:**1294 (Dec.) 1936.

The most constant changes were (*a*) symmetric diminution in the size of the scapulas, (*b*) rather large humeral heads in relation to the small, shallow glenoid fossae, (*c*) slender humeral shafts, in some instances approaching the "pipe-stem" appearance, with widened medullary canals and thin, but not atrophic, cortices and (*d*), in several instances, disproportionately slender femurs, tibias, fibulas, radiuses and ulnas, which showed the same type of change seen in the humeri.

The pelvis was small in all the patients, with flaring iliac bones, prominent ischial spines and marked coxa valga. These changes, aside from the coxa valga, may be accounted for by the fact that the patients

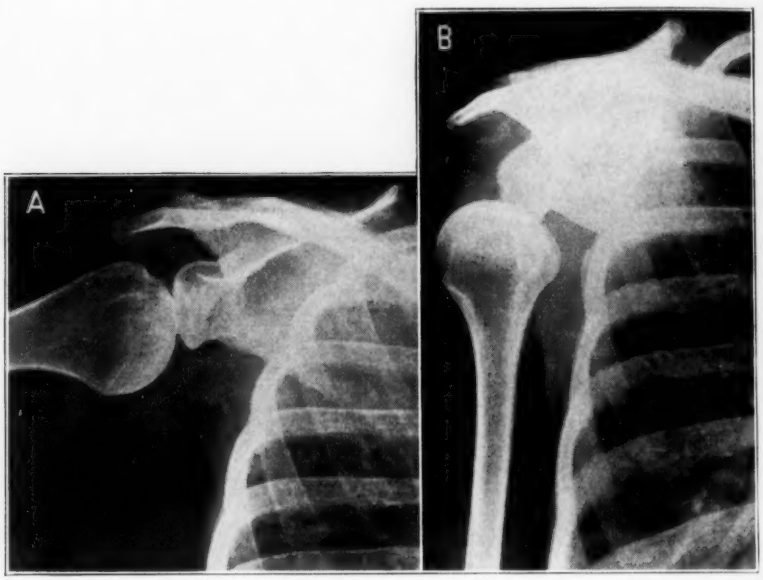

Fig. 3.—*A* (case 7): The right scapula is small and the humeral head large as compared with the glenoid fossa. *B* (case 7): The shoulder joint with the arm in the pendant position. Note the slender humeral shaft.

had spent many years in wheel chairs, as a result of their disease. This supposition is supported by the roentgenographic examination of the pelvis of a patient with hypertrophic muscular dystrophy who is still ambulatory. It is noteworthy that his pelvis was of normal configuration and that he, too, had coxa valga.

No definite relation could be established between the size of a limb and its bony structure. In some instances in which the contours were either normal or pseudohypertrophic the bones were slender, while in others in which muscular atrophy was the outstanding feature the architecture of the bone was relatively normal. Neither was there a

definite relation between the patient's slight ability to move and the size of the skeletal structures. Pathologic fractures were not noted. In several patients the normal fascial planes seen in the soft tissues were replaced by a diffuse haze.

Interpretation of the alterations is difficult with present knowledge of this condition. It is doubtful that the osseous changes are due to disuse. The usual changes associated with disuse of a limb, such as are seen after immobilization in a cast, are rarefaction and decalcification of the bone, particularly the articular ends. In our cases these changes did not occur. Atrophy of disuse is progressive, whereas in our cases

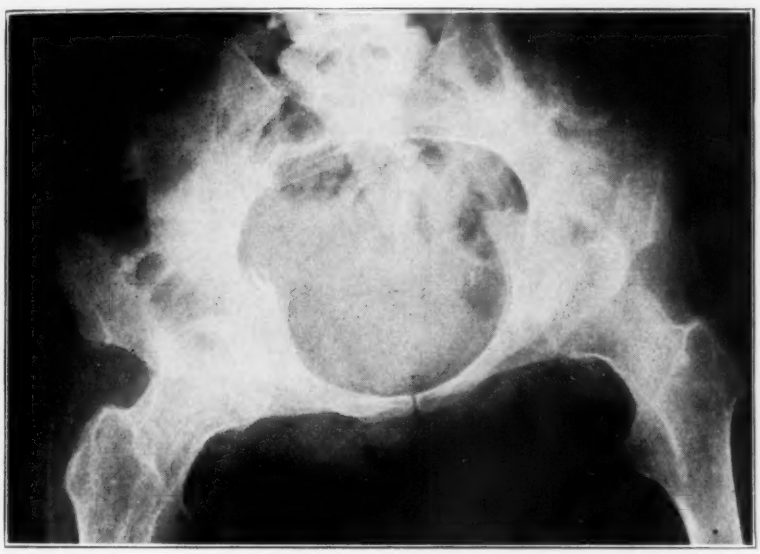

Fig. 4 (case 6).—The pelvis is small, both iliac bones are flared and the ischial spines are sharp and prominent. There are marked coxa valga and diminution in the articular space between the femoral head and the acetabular fossa.

serial studies showed no progressive loss of density of the bone over a period of years.

Again, an attempt to compare the changes with those seen after poliomyelitis is unsatisfactory, since in the latter condition some shortening of the bone as well as rarefaction occurs. Nor is there any similarity to the changes seen in osteomalacia, in which changes in the bony structures are extensive.

Parathyroid dyscrasias usually result in cystic disease of bone, which produces roentgenographic changes quite different from those reported here. Celiac disease may also produce changes in bone of an atrophic nature, usually resembling those seen with osteoporosis of disuse.

CONCLUSION

The older view that muscular dystrophy is a disease which involves muscle only may have to be revised to include the concept of a more generalized pathologic process. In addition to the alterations in creatinine and carbohydrate metabolism and the possible disturbance of the endocrine glands, there is involvement of bone, as indicated by our roentgenographic studies.

It is our opinion that the changes cannot be explained on the basis of disuse alone, but may be an expression of a mesodermal defect, resulting in muscular and skeletal defects.

TOPICAL ARRANGEMENT WITHIN THE SPINOTHALAMIC TRACT OF THE MONKEY

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It was Spiller [1] who first observed that painful and thermal sensations are carried within the anterolateral columns of the spinal cord and that surgical section of the anterolateral part of the cord will result in contralateral analgesia and thermanesthesia below the lesion. From surgical experiences gained as a result of the application of this remarkable observation Foerster and Gagel,[2] Hyndman and Van Epps [3] and Walker [4] have amplified Spiller's observations and have suggested that the fibers from different levels of the spinal cord are segmentally organized within the anterolateral columns and within the brain stem. The present study was undertaken to determine the topical arrangement of the fibers within the spinothalamic tract in the monkey.

METHOD OF STUDY

Using anesthesia induced by pentobarbital sodium and aseptic technic, unilateral anterolateral chordotomies were made in 6 Macacus rhesus monkeys at different levels of the spinal cord, from the upper cervical to the lower lumbar region. In 5 additional animals midline myelotomies (Putnam [5]) involving one spinal segment were performed at different levels (table). Figure 1 shows the site and extent of a typical lesion. The chordotomies were designed to section all white matter in the anterolateral funiculus of the spinal cord ventral to the attachment of the dentate ligament. The myelotomies were made just to one

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This research was aided by a grant from the Douglas Smith Foundation.

1. Spiller, W. G.: The Location Within the Spinal Cord of the Fibers for Temperature and Pain Sensation, J. Nerv. & Ment. Dis. **32**:318-320, 1905.

2. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

3. Hyndman, O., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract, Arch. Surg. **38**:1038-1053 (June) 1939.

4. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298 (Feb.) 1940.

5. Putnam, T. J.: Myelotomy of the Commissure: A New Method of Treatment for Pain in the Upper Extremities, Arch. Neurol. & Psychiat. **32**: 1189-1193 (Dec.) 1934.

side of the midline and were designed to interrupt all of the fibers crossing in the anterior commissure in one segment of the cord. The animals were killed from fourteen to eighteen days after operation, and the spinal cords and brains

Experimental Data on Eleven Monkeys Subjected to Chordotomy or Myelotomy

Animal No.	Site of Chordotomy *	Site of Myelotomy
1	.....	T 6-7
2	T 6 right	.....
3	T 12 right	.....
4	C 3 right	.....
4	.....	C 5-7
6	L 2 right	L 1-2
7	L 3 right	.....
8	C 5 right	.....
9	.....	C 4-6
10	.....	T 11-12
11	L 1 right	.....

* In this table, C indicates the cervical region of the cord; T, the thoracic region, and L, the lumbar region.

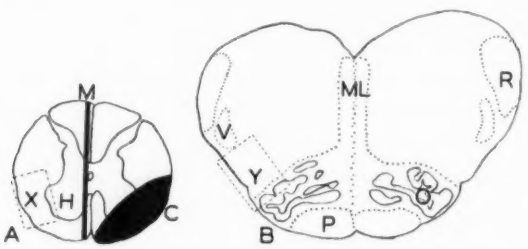

Fig. 1.—*A*, outline drawing of a cross section of the cervical portion of the spinal cord of the macaque to show the types of experimental lesions and the area (*X*) from which the photomicrographs shown in figure 2 were taken.

B, outline drawing of a cross section of the medulla oblongata at the level of the inferior olivary nucleus to show the area (*Y*) from which the photomicrographs in figure 3 were taken.

The following abbreviations are used in this illustration: *C*, portion of the cord involved in anterolateral chordotomy; *H*, substantia grisea, columna anterior; *M*, portion of the cord involved in midline myelotomy; *M L*, lemniscus medialis; *O*, nucleus olivaris; *P*, tractus pyramidalis; *R*, corpus restiforme; *V*, tractus spinalis, nervi trigemini; *X*, area within dotted rectangle representing the portion of the anterolateral column photomicrographed in figure 2; *Y*, area within dotted rectangle representing the portion photomicrographed in figure 3.

were treated by the Marchi method as outlined by Walker.[4] The area of the lesion and the thalamus of each animal were cut serially, and representative sections were made from blocks taken from several other levels of the spinal cord and brain stem.

RESULTS

The anterolateral chordotomies appeared to be complete in every instance. Each of the myelotomies had severed all of the fibers crossing

the midline in the anterior commissure at the involved segment. In addition, in 2 of the 5 cases the ventral part of the lesion extended rather far laterally, so that a major portion of the ipsilateral lateral column was destroyed. In these cases, then, there was a fortuitous chordotomy on one side with interruption of the entire spinothalamic tract, whereas on the opposite side only that part of the tract arising from one segment was injured.

It is well established that pain and temperature fibers enter the spinal cord through the posterior roots, synapse in the dorsolateral gray matter and send secondary axons through the anterior commissure to the anterolateral column of the contralateral side. This anterolateral column of ascending fibers is composed of spinobulbar, spinotectal and spinothalamic fibers and occupies the portion of the cord inferior to the dentate ligament and extends anteriorly almost to the midline. It should be understood that while we refer only to degeneration of the spinothalamic tracts, it is impossible to separate the degeneration of these three tracts in the spinal cord. Thus the localization which we demonstrate is one of all three tracts.

A study of the degeneration following myelotomy shows that after crossing in the anterior commissure the fibers at first lie just lateral to the anterior gray column. As they ascend in the cord they pass more and more toward the periphery until in the cervical region they assume their most lateral position. In general the fibers from the sacral and lumbar segments lie on the extreme periphery and slightly more dorsal than those from the thoracic and cervical segments, although there is no absolute segmental lamination. The topical arrangement is present at all levels of the spinal cord but is more easily seen in the cervical region. The degeneration in this region resulting from a midthoracic chordotomy is intense along the periphery of the anterolateral funiculus (fig. 2*A*); after a myelotomy in the same part of the thoracic portion of the cord the degeneration is more intense in a linear zone some distance from the periphery in an area which corresponds to the medial part of the degeneration seen after a midthoracic chordotomy (fig. 2*B*). After a low cervical myelotomy the degenerated fibers at the midcervical segment lie along the lateral margin of the anterior horn (fig. 2*C*), while as a result of a low cervical chordotomy the degeneration reaches from the anterior horn to the periphery of the spinal cord (fig. 2*D*).

There also appears to be a topical arrangement of the tract within the medulla oblongata. A low cervical chordotomy produces an area of intense degeneration lying close to the surface of the medulla oblongata just dorsolateral to the inferior olive. Medial to the base of the triangle there are degenerated fibers visible for some little distance into the substance of the brain stem (fig. 3*A*). After a midthoracic chordotomy only the peripheral and inferior portion of the triangle shows intense

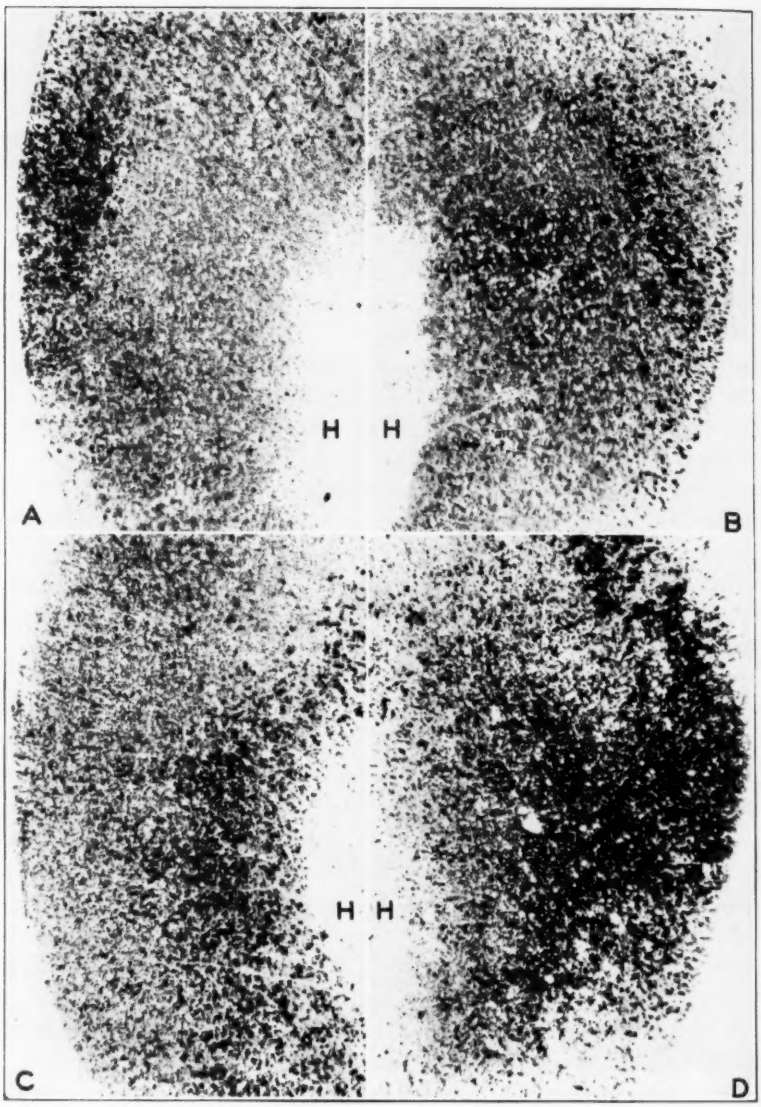

Fig. 2.—Unretouched photomicrographs of the lateral funiculi in the mid-cervical region of the spinal cord. *A* shows degeneration resulting from a mid-thoracic chordotomy; *B*, degeneration resulting from a midthoracic myelotomy; *C*, degeneration resulting from a low cervical myelotomy; *D*, degeneration resulting from a low cervical chordotomy. *H* is the substantia grisea, columna anterior.

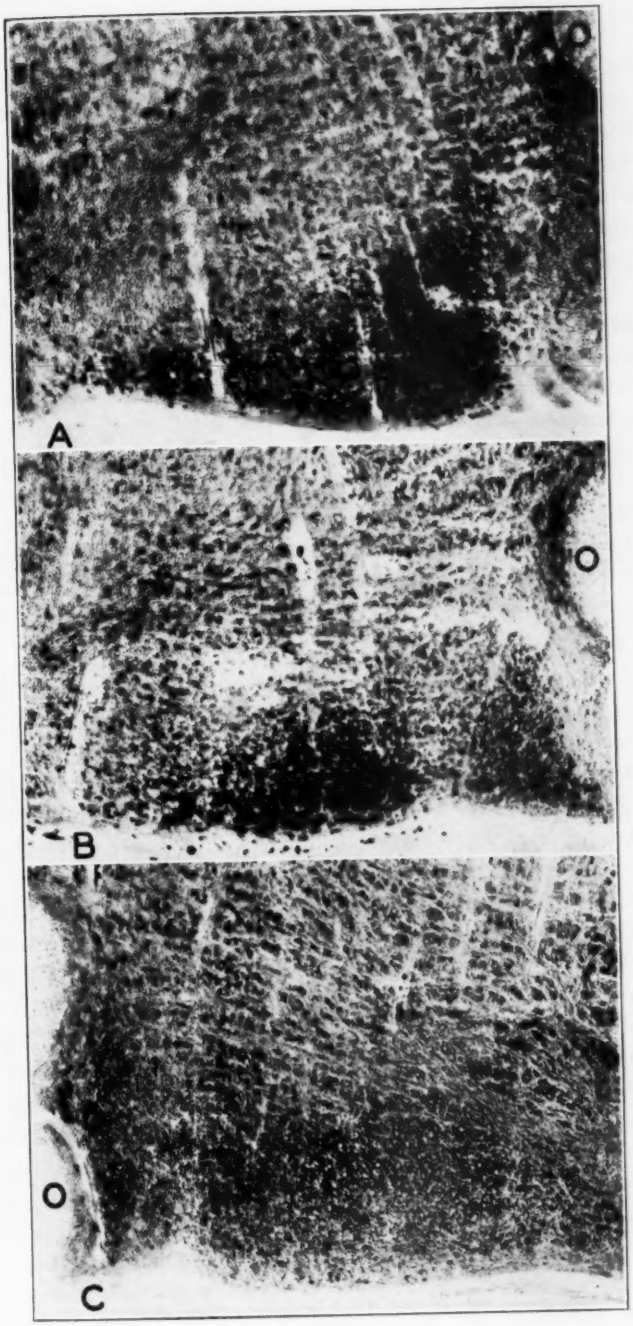

Fig. 3.—Unretouched photomicrographs of the region of the lateral reticular nucleus at the level of the middle of the olive. *A* shows degeneration resulting from a low cervical chordotomy; *B*, degeneration resulting from a midthoracic chordotomy; *C*, degeneration resulting from a midcervical myelotomy. *O* is the nucleus olivaris.

degeneration and almost no fibers extend into the medullary substance medial to the base (fig. 3 *B*). A midcervical myelotomy produces degenerated fibers superior to the inferior olive some distance from the lateral surface of the medulla oblongata, with relatively little degeneration near the surface (fig. 3 *C*).

We have followed the course of the fibers farther rostrally through the pons and mesencephalon and to their final termination in the nucleus ventralis posterior of the thalamus, but we have not been able to determine a precise segmental arrangement of the fibers. It did appear that after lumbar chordotomy the degenerated fibers terminated laterally in the nucleus ventralis posterolateralis of the thalamus and that after cervical chordotomy there were more degenerated fibers medially in this nucleus. But after cervical myelotomies the degeneration was not confined to the medial part of the nucleus ventralis posterolateralis. Perhaps this was due to degenerated fibers passing through the lateral part of the nucleus to end in its medial half. This finding makes it impossible to conclude from the present experiments the precise topical termination of the spinothalamic fibers.

COMMENT

The segmental arrangement of the fibers of the spinothalamic tract in the spinal cord as determined by this study for the monkey is similar to that for man. The peripheral situation of the fibers from the sacral and lumbar segments has been emphasized by Foerster and Gagel,[2] and the dorsal shifting of these fibers at higher levels of the spinal cord, by Hyndman and Van Epps [3] and Walker.[4] This arrangement of these fibers explains certain sensory phenomena seen after chordotomy. Occasionally the sacral segments are not analgesic, although the higher segments of the lumbar and thoracic regions are completely insensitive to painful stimuli. If the sacral segments lay evenly on the periphery of the cord it would be difficult to avoid sectioning them when the deeper lying fibers are cut, but the fact that they also lie dorsally makes it possible for an anteriorly placed incision to sever only the fibers from the higher segments.

That there exists an arrangement of the fibers in the human medulla oblongata similar to that demonstrated by this study for the monkey seems probable from the observations of Walker [4] and the surgical experiences of Schwartz and O'Leary [6] with medullary tractotomy. Our studies indicate that in the monkey a medullary tractotomy designed to produce contralateral analgesia must necessarily be carried rather deep within the substance of the medulla oblongata to include the fibers

6. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway for Pain, Surgery **9**:183-193, 1941.

arising from higher segmental levels. A more superficial section would interrupt only the fibers from the lower extremities—a result which can be obtained by a less dangerous low cervical or thoracic chordotomy.

The entire spinothalamic tract lies very superficially in the mesencephalon.[7] At this level the secondary trigeminal pathways carrying pain and temperature sensations from the face are slightly inferiorly and medially placed. The proximity of these pathways and their peripheral situation in the mesencephalon make them accessible for surgical section. Dogliotti [8] has had favorable clinical results from interruption of the pain tracts in the upper part of the pons; we [9] have successfully cut these fibers in the mesencephalon.

It seems probable that a topical localization exists in the spinothalamic tract in the pons and mesencephalon, although we are unable to demonstrate it by the present experimental method. Our experiences with mesencephalic tractotomy in man favor this view, for after section of the pain pathways in the mesencephalon we have observed practically complete analgesia of the face, arm and trunk on the contralateral side but little sensory impairment of the legs.

SUMMARY

The course and localization of the spinothalamic tract were traced in 11 monkeys after anterolateral chordotomies and midline posteroanterior myelotomies had been performed at different levels of the spinal cord.

In general, as higher levels in the spinal cord are reached, fibers from lower segments tend to become concentrated laterally and dorsally within the anterolateral column and fibers from higher levels are situated more medially and inferiorly, although there is no absolute segregation at any level. Within the medulla, fibers from the lower levels are concentrated at the periphery of the bulb, whereas fibers from the cervical region lie medially. Although there is evidence that such an arrangement exists, the topical localization of the fibers in the pons, the midbrain or within the nucleus ventralis posterior of the thalamus could not be demonstrated by the methods used in this investigation.

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7. Clark, W. E. L.: The Termination of the Ascending Tracts in the Thalamus of the Macaque Monkey, J. Anat. **71**:7-40, 1936. Walker.[4]

8. Dogliotti, M.: First Surgical Sections in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145, 1938.

9. Unpublished data.

METRAZOL CONVULSIONS IN THE TREATMENT OF THE PSYCHOSIS OF DEMENTIA PARALYTICA

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It is a common clinical experience in the treatment of dementia paralytica that despite serologic improvement following the usual treatments for syphilis, patients often remain psychotic. One of us (V. B. K.) suggested that metrazol shock therapy, which has proved beneficial in cases of the functional psychoses, might yield similar results in cases of the psychosis of dementia paralytica. After favorable results had been achieved in 1 such case,[1] metrazol shock therapy was administered in 15 other cases. The data on this group and the results obtained are reported.

MATERIAL AND METHOD

The group consisted of 12 patients with dementia paralytica who had previously received chemotherapy and hyperpyrexia without substantial improvement of the psychotic symptoms and of 4 patients who had received neither chemotherapy nor hyperpyrexia. At the time metrazol treatment was instituted the psychotic syndromes of the first 12 patients appeared to be stabilized. The last 4 patients were selected to demonstrate whether metrazol therapy alone could influence the psychosis of dementia paralytica. In the cases of these 4 persons the metrazol therapy was followed by the necessary hyperpyrexia and chemotherapy. In none of the cases did we feel justified in withholding all antisyphilitic treatment during the course of metrazol therapy. In order to minimize extraneous factors—the effect of tryparsamide, for example—chemotherapy was limited to the administration of an aqueous solution of bismuth sodium tartrate, 0.06 Gm. twice a week.

Table 1 summarizes the neurologic findings on admission, the amount of chemotherapy and of hyperpyrexia given prior to the administration of metrazol, the interval between the cessation of hyperpyrexia and the administration of metrazol, the number and length of convulsions, the dosage and the psychiatric clinical results. Table 2 presents the serologic reactions present on admission and those observed

1. Kenyon, V. B., and Rapaport, D.: The Etiology of the Psychosis of Dementia Paralytica with a Preliminary Report of the Treatment of a Case of This Psychosis with Metrazol, J. Nerv. & Ment. Dis. **94**:147-159, 1941.

before and after induction of the series of metrazol convulsions. As a further control on the clinical evaluation of the results, psychologic tests (the Rorschach [2] and the Babcock deterioration [3] test) were administered to the patients, both before and after the course of metrazol treatments. Brief psychiatric descriptions with summaries of the psychologic observations will be found in table 3.

RESULTS OF THE SHOCK TREATMENT

In this group of patients with dementia paralytica neither the dose of metrazol necessary to produce convulsions nor the duration of the seizures elicited differed appreciably from that for patients with functional psychoses (Katzenelbogen and associates [4]). Despite the justified fear that the artificial production of convulsions in a condition such as dementia paralytica, with its organic damage and known tendency to produce in itself convulsive seizures, would be likely to result in further damage to the brain, no exacerbations of the neurologic signs followed the treatment in this series of cases. Furthermore, laboratory studies (table 2), particularly of the spinal fluid, made before the institution of the convulsive treatment and shortly after its completion, showed that in 8 of the cases (2, 7, 8, 11, 12, 13, 14 and 15) there was moderate reduction in the number of cells. However, in only 1 of these cases (14) was the initial number of cells much elevated before the metrazol treatment, and only in 2 cases (4 and 16) was there an increase in the number of cells. In case 16 the increase was especially significant despite marked clinical improvement.

The colloidal gold tests indicated a slight flattening of the curves in 4 cases (2, 6, 12 and 15) and noticeable heightening in 5 cases (4, 5, 7,

2. The Rorschach test is a so-called projective test. The patient is shown ten ink blots (part dark, part light, in color) and asked "What might this be?" The formal properties of the responses given have been found to correspond to personality characteristics of the subject. The adequacy of the interpretations given and the ability to choose obvious parts of the blots for interpretation reflect the subject's soundness of judgment and intellectual functioning. The responses influenced by colors represent his affectivity and rapport; different kinds of such color influences may reflect adaptive, labile and impulsive affectivity, and the like. Responses describing human movements reflect the vividness of psychomotility—in psychotic patients, the intensity and degree of systematization of delusions. These few points do not exhaust the potentialities of the test, but will shed some light on the way the aforementioned responses were derived.

3. The Babcock deterioration test consists of simple tests for recent and remote memory, motor ability and vocabulary. The test is built on the experience that of these vocabulary deteriorates the least. The test scores corresponding to different vocabulary scores for normal subjects were statistically established. The difference between the patient's actual scores and the scores equivalent to his vocabulary score for normal persons gives the deterioration scores tabulated.

4. Katzenelbogen, S.; Brody, M. W.; Hayman, M., and Margolin, E.: Metrazol Convulsions in Man, Am. J. Psychiat. **95**:1343, 1939.

TABLE 1.—*Clinical Data on Sixteen Patients Given Metrazol Treatment*

Patient, Age, Sex	Neurologic Findings on Admission	Treatment Prior to Metrazol: Hyperpyrexia	Treatment Prior to Metrazol: Chemotherapy *	Interval Between Hyperpyrexia and Metrazol	Period of Treatment; Number of Convulsions	Length of Convulsion, Seconds	Dosage, Range in Cc.	Clinical Results (Psychiatric)
1 A. Cl. 25 M	Pupils normal; deep reflexes exaggerated	Malaria and artificial fever 41 hours.....over 103 F. 38 hours.....over 104 F.	Bis..... 1.32 Gm. Tryp...30.00 Gm. Merc.... 1.00 Gm.	80 days	8/10/39-9/21/39 13 convulsions	Not recorded	4-7	Excellent improvement; paroled from hospital
2 C. M. 46 M	No pupillary changes; right patellar reflex absent; slight dysarthria	Artificial fever 55 hours.....over 104 F. 28 hours.....over 105 F.	Bis..... 0.96 Gm. Tryp...25.50 Gm.	40 days	10/20/39-11/24/39 11 convulsions	50 to 75	3-8.2	Good improvement; paroled from hospital
3 L. B. 30 F	No pupillary changes; deep reflexes exaggerated	Malaria 52 hours.....over 104 F. 35 hours.....over 105 F.	Bis..... 1.02 Gm. Tryp...34.50 Gm.	81 days	11/11/39-2/6/39 26 convulsions	45 to 65	4.5-7.5	Change in psychotic symptoms during treatment; stabilized improvement after reinoculation with malaria
4 E. C. 33 F	No pupillary changes; dysarthria marked	Artificial fever 53 hours.....over 105 F. 26½ hours.....over 106 F.	Bis..... 0.42 Gm. Tryp...57.00 Gm. Merc.... 1.50 Gm.	102 days	11/11/39-1/16/40 20 convulsions	40 to 60	4.5-10.0	No change
5 I. C. 40 F	Pupils react to light, not accommodation; dysarthria; tremors of fingers	Malaria and typhoid 39 hours.....over 103 F. 23 hours.....over 104 F. 7 hours.....over 105 F.	Neo..... 3.30 Gm. Tryp... 4.00 Gm. Bis..... 0.12 Gm.	20 mo. and 20 days	11/17/39-1/12/40 16 convulsions	50 to 60	5-9.8	Initial improvement; then partial relapse; stabilized improvement only after cessation of metrazol
6 A. C. 46 M	Pupils irregular; sluggish to light and accommodation; dysarthria; marked optic atrophy	Artificial fever, 2 courses 111 hours.....over 104 F. 70 hours.....over 105 F.	Bis..... 1.20 Gm. Tryp...57.00 Gm. Merc.... 0.65 Gm.	5 mo. after 1st course, 3 wk. after 2d course	12/15/39-2/2/40 15 convulsions	Not recorded	4.5-8	No change
7 L. G. 37 M	Seventh nerve paralysis on right (typhoid in childhood); pupils normal; dysarthria; positive Romberg sign; deep reflexes exaggerated; Babinski positive	Artificial fever 57 hours.....over 104 F. 44 hours.....over 105 F.	Bis..... 1.02 Gm. Tryp...42.00 Gm.	80 days	10/24/39-12/12/39 14 convulsions	45 to 70	4.5-9.8	Slight improvement but relapse 2 mo. after cessation of metrazol

8	O. B. G. 53 M	Pupils constricted, right sluggish to light	Malaria 26 hours.....over 103 F.	Bis..... 1.02 Gm. Tryp...16.50 Gm.	39 days	10/20/39-12/26/39 18 convulsions	30 to 70	5-10	No change
9	M. L. 34 F	No pupillary changes; positive Babinski sign on right	Malaria 38 hours.....over 104 F. 21 hours.....over 105 F.	Neo..... 6.80 Gm. Bis..... 0.24 Gm. Tryp...15.00 Gm.	14 mo.	11/17/39-11/28/39 4 convulsions	40 to 45	3.5-4.3	Improvement; relapse 10 weeks after cessation of metrazol
10	J. McA. 33 M	Pupils unequal and irregular; left pupil fixed; ataxic; positive Romberg sign; absence of patellar and achilles reflexes; dysarthria	Artificial fever 63 hours.....over 104 F. 46 hours.....over 105 F.	Bis..... 1.32 Gm. Tryp...25.50 Gm. Merc.... 0.70 Gm.	30 days	10/20/39-1/9/40 22 convulsions	32 to 75	4-11	Change in psychotic symptoms during treatment; no lasting improvement
11	R. N. 34 M	Pupils fixed and irregular; ataxic; positive Romberg sign; absence of patellar reflexes; marked dysarthria	Artificial fever and malaria 85 hours.....over 104 F. 60 hours.....over 105 F.	Bis..... 1.32 Gm. Tryp...51.00 Gm. Merc.... 2.40 Gm.	6 mo. after artificial fever, 6 wk. after malaria	10/20/39-12/26/39 20 convulsions	40 to 75	4-10	No change
12	R. Z. 39 M	Pupils unequal and fixed; dysarthria; slightly exaggerated reflexes	Artificial fever and malaria 51 hours.....over 104 F. 26 hours.....over 105 F.	Bis..... 0.82 Gm. Tryp...35.00 Gm.	97 days	10/20/39-12/22/39 18 convulsions	35 to 65	5-11.8	Slight improvement; relapse after treatment
13	P. O. 42 M	Pupils sluggish to light; hyperactive reflexes; coarse tremors of fingers	Malaria following metrazol 52 hours.....over 104 F. 20 hours.....over 105 F.	During metrazol treatment, bis. 1.08 Gm.	No previous fever	11/28/39-1/23/40 17 convulsions	Not recorded	5-11	Improvement
14	H. K. 51 F	Pupils fixed and irregular; hyperactive reflexes; dysarthria	Postmetrazol artificial fever 100 hours.....over 105 F. 65 hours.....over 106 F.	During metrazol treatment, bis. 1.20 Gm.	No previous fever	11/11/39-1/16/40 20 convulsions	50 to 70	5-8.8	No change
15	E. G. 39 F	Pupils irregular; slight dysarthria	Postmetrazol artificial fever 53 hours.....over 105 F. 32 hours.....over 106 F.	During metrazol treatment, bis. 0.90 Gm.	No previous fever	11/11/39-1/15/40 11 convulsions	35 to 65	5-6.5	Good improvement; paroled after subsequent hyperpyrexia
16	H. J. 32 M	Pupils slightly irregular; hyperactive reflexes; dysarthria; slight dysdiadokokinesis	Postmetrazol artificial fever 65 hours.....over 105 F. 32 hours.....over 106 F.	During metrazol treatment, bis. 0.96 Gm.	No previous fever	10/20/39-12/1/39 13 convulsions	40 to 60	4-8.6	Good improvement; paroled after subsequent hyperpyrexia

*"Bis." indicates bismuth sodium tartrate; "Tryp." tryparsamide; "Neo." neoarsphenamine, and "Merc.," mercurosal (disodium hydroxymercurisalicyloxyacetate).

TABLE 2.—*Summary of Serologic Reactions Before and After Metrazol Therapy*

Patient	Serologic Reactions on Admission					Serologic Reactions Prior to Metrazol					Serologic Reactions After Metrazol				
	Blood		Spinal Fluid			Blood		Spinal Fluid			Blood		Spinal Fluid		
	Kolmer	Kahn	Kolmer	Cells per Cu. Mm.	Colloidal Gold Curve	Kolmer	Kahn	Kolmer	Cells per Cu. Mm.	Colloidal Gold Curve	Kolmer	Kahn	Kolmer	Cells per Cu. Mm.	Colloidal Gold Curve
1. A. C.	3/15/39 +	+	+	15	3334322100	..	..	..	..	.....	9/11/39 +	+	+	6	0000000000
2. C. M.	7/24/39 +	+	+	94	5555532100	9/25/39 +	+	+	15	4443221000	11/27/39 +	+	+	7	3344332110
3. L. B.	8/4/39 +	+	+	..	5555432110	10/23/39 +	+	+	6	3321100000	3/1/40 +	+	+	4	3332100000
4. E. C.	6/20/39 +	?	+	11	5555433210	9/29/39 +	+	+	1	2211000000	1/26/40 —	—	+	11	3334321100
5. I. C.	2/23/38 +	+	+	..	5555552100	10/23/39 +	?	+	1	0000000000	1/31/40 —	—	+	1	1122100000
6. A. C.	6/14/39 +	+	+	26	5555553200	12/8/39 +	+	+	2	5555432100	2/9/40 +	+	+	3	5444321000
7. L. G.	6/28/39 +	+	+	6	5555542210	10/16/39 +	+	+	10	1111221100	1/5/40 +	+	+	5	3344221000
8. O. B. G.	8/2/39 +	+	+	47	5555543210	10/16/39 +	+	+	15	1112110000	1/29/40 +	+	+	11	3333210000
9. M. L.	9/9/37 —	+	—	..	1112200000	10/23/39 — Kline 4+	—	—	0	0000000000	3/4/40 — Kline 33+	— Kahn 1+	—	0	0000000000
10. J. McA.	7/31/39 +	+	+	20	5555542100	10/16/39 +	+	+	6	0000000000	1/15/40 +	+	+	8	1112221000
11. R. N.	3/1/39 +	?	+	37	5555555322	10/16/39 +	+	+	12	1112210000	1/13/40 +	+	+	1	1112211100
12. R. Z.	2/20/39 +	+	+	6	5555554332	10/10/39 +	+	+	6	5432100000	1/13/40 +	+	+	1	4432210000
13. P. O.	10/16/39 +	+	+	17	5432210000	..	..	..	..	.....	1/29/40 +	+	+	7	5555321000
14. H. K.	10/30/39 +	+	+	40	5554310000	..	..	..	..	.....	12/30/39 +	+	+	3	5554321000
15. E. G.	10/16/39 +	+	+	11	5554321000	..	..	..	..	.....	12/26/39 +	+	+	5	4432211000
16. H. J.	10/9/39 +	+	+	14	5555421000	..	..	..	.	.....	12/4/39 +	+	+	41	5555544321

8 and 10), but in none of these instances was there elevation to the height of the initial curves obtained on admission. The significance of these changes occurring during metrazol therapy is at present unclear. The elevations of the colloidal gold curves may have been due either to the metrazol convulsions or to other factors. We found that patients with dementia paralytica undergoing intensive antisyphilitic therapy at times show similar elevations in the colloidal gold curves.

In 2 cases (4 and 5) the Kolmer and Kahn reactions of the blood, previously positive, were negative after the metrazol treatment, while the colloidal gold curves showed elevation.

Thus, the results of examinations in this group immediately and six months after termination of the metrazol treatment appear to present no evidence that the convulsive therapy exerted significant deleterious effects. The material obtained by psychologic testing seems to corroborate grossly this conclusion (table 3).

ANALYSIS OF CASES

A number of the cases appear worthy of special mention and are divided into groups having certain features in common: groups I, II and III include the cases in which previous treatment with hyperpyrexia was given, and group IV is comprised of cases in which no treatment was given.

GROUP I.—In cases 1 and 2 only slight improvement followed hyperpyrexia. After metrazol treatment the improvement was sufficient to warrant parole. Case 1, that of A. C., has been described in detail elsewhere.[1]

CASE 2.—C. M., aged 46, a Works Progress Administration foreman, on admission had evidenced confusion and grandiose delusions concerning his inventive ability. In the course of hyperpyrexia he became oriented and cooperative, but was still evasive, anxious and grandiose, with little insight. He exhibited extreme apprehension before each metrazol treatment. In the early part of the series the convulsions were followed by marked hysterical phenomena, with acute terror and thoughts of impending death. This reaction and his grandiose ideas later disappeared; the evasiveness decreased; considerable insight developed, and he was paroled one month later.

GROUP II.—In cases 3, 5 and 10 the initiation of metrazol therapy produced some improvement; further treatment resulted in distinctly unfavorable symptoms, which, however, in 2 of the cases disappeared shortly after cessation of the treatments. This sequence of events also seems to demonstrate that convulsive therapy has some effect on the psychosis associated with dementia paralytica.

CASE 3.—L. B., aged 30, a waitress, on admission was disoriented, confused and filthy and had auditory and visual hallucinations. After induction of malaria she became tidy and cooperative, but continued to be seclusive and disoriented as

TABLE 3.—*Summary of Psychiatric Evaluations and Results of Psychologic Tests*

Patient	Psychiatric Evaluations: Before Metrazol Treatment	Psychiatric Evaluations: After Metrazol Treatment	Rorschach Evaluations *: Before Metrazol Treatment	Rorschach Evaluations *: After Metrazol Treatment	Results of Babcock Deterioration Test †: Before Metrazol Treatment	Score	Results of Babcock Deterioration Test †: After Metrazol Treatment	Score
1 A. Cl.	8/1/39: Self-accusatory delusions; no insight; mode of infection confabulated; psychomotor retardation. Oriented; uncooperative in ward	10/1/39: Disappearance of delusions; good insight and improved judgment; normal psychomotor activity; adequate emotional responses. Cooperative	9/10/39: Simple schizophrenic-like picture with delusions, blocking and intense bodily preoccupation (test given during course of treatment)	9/24/39: Blocking and bodily preoccupation decreased; first appearance of emotional adaptivity and rapport. Improvement like that of catatonic and simple schizophrenic patients ‡	No test given		General mental eff. fair Recent memory eff. very good Remote memory eff. poor Motor eff. rather poor	—0.5 +1.7 —1.1 —0.6
2 C. M.	10/21/39: Evasiveness; anxiety; slight insight; impaired judgment; furtiveness. Oriented	12/7/39: Less anxiety; improved insight; improved judgment; better social rapport. Oriented; less evasive	9/28/39: Test reactions resemble those of an evasive, paranoid schizophrenic patient. Absence of free affective reactions; judgment impaired	11/29/39: Evasiveness decreased; first signs of emotional rapport; judgment much improved; picture still schizoid	General mental eff. path. poor Recent memory eff. poor Remote memory eff. path. poor Motor eff. path. poor	—5.0 —1.3 —6.0 —5.6	General mental eff. poor but improved Recent memory eff. decreased Remote memory eff. poor but improved Motor eff. poor but improved	—3.7 —2.0 —3.1 —4.4
3 L. B.	11/4/39: Marked illusions; hallucinations; grandiose delusions. Oriented to time; suspicious. Acknowledges infection but has no insight	3/20/40: No stable improvement; transitory periods of better touch with reality. More negativistic	11/1/39: Test reactions resemble those of an evasive, paranoid schizophrenic patient, with rich delusional content. Some "organic" indications	Patient became combative when asked to take the test and refused to take it	General mental eff. very poor Recent memory eff. poor Remote memory eff. path. poor Motor eff. good	—2.8 —1.5 —4.5 —0.2	Patient refused test. Her general alertness suggested, however, that the deterioration had improved	
4 E. C.	10/10/39: Restless, evasive, flighty; oriented. Marked intellectual and emotional blunting; no insight	1/18/40: No appreciable change	9/28/39: Judgment extremely impaired. Emptiness and narrow range of interests; very labile mood. Responses resemble those of feebleminded person	1/19/40: Intellectual impairment and emptiness even more marked; mood slightly less labile	General mental eff. path. poor Recent memory eff. path. poor Remote memory eff. path. poor Motor eff. very poor	—5.2 —3.2 —7.5 —2.0	General mental eff. path. poor Recent memory eff. path. poor Remote memory eff. path. poor Motor eff. very poor	—5.9 —4.1 —7.0 —3.0
5 I. C.	11/16/39: Partial orientation; delusions of grandeur; slight insight; flight of ideas. Euphoric. Does no work	3/8/40: Shows better stability; helps well with ward work. Fewer delusions	11/3/39: Judgment extremely impaired. Very flighty, with strong bodily preoccupations and anxieties	1/4/40: Flightiness increased to a degree of extreme confusion; bodily preoccupations decreased. Otherwise unchanged and empty	General mental eff. path. poor Recent memory eff. very poor Remote memory eff. path. poor Motor eff. path. poor	—6.6 —2.2 —6.7 —6.2	No test given; patient uncooperative	

6 A. C.	12/19/39: Impaired memory; no insight; intellectual and emotional blunting. Denies infection. Irritable; depressed; disoriented	2/9/40: Increased visual impairment; more marked delusions with confabulation. Easily angered; better oriented	12/6/39: Responses show confusion and delusional confabulation with many "organic" indications	Patient failed to respond to test because of visual impairment	General mental eff. path. poor.....—9.4 Recent memory eff. very poor.....—4.6 Remote memory eff. path. very poor—11.6 Motor eff. path. very poor.....—12.6	No test given owing to visual impairment
7 L. G.	10/19/39: Very negativistic; depressed; confused; disoriented; filthy; asocial. No insight; nihilistic delusions	1/13/40: Less negativistic; less depressed; better oriented; less filthy. Constructive fantasying; no delusions; no insight. Later relapsed	10/19/39: Blocking and anxiety-charged delusions; lack of rapport; very low level of intellectual functioning	12/24/39: Anxiety-charged delusions disappear. Slight decrease of blocking and withdrawal symptoms. No improvement of rapport. Intelligence improved but still low	Patient refused to be tested and displayed impotent rage on being confronted with tasks he could not cope with	General mental eff. path. poor.....—5.0 Recent memory eff. poor.....—1.7 Remote memory eff. path. poor.....—4.0 Motor eff. weak.....—0.1
8 O. B. G.	10/10/39: Denies infection. Blocked; disoriented. Poor recent memory with confabulations; unorganized delusions of grandeur; depression	1/18/40: Less depressed. Otherwise no change	10/13/39: Emptiness; impaired judgment; absence of rapport	2/15/40: Orientation and judgment slightly improved. Slight traces of rapport appear	General mental eff. path. poor.....—7.3 Recent memory eff. path. poor.....—4.7 Remote memory eff. path. very poor—7.4 Motor eff. path. poor.....—5.1	General mental eff. path. but improved—5.4 Recent memory eff. very poor.....—4.3 Remote memory eff. much improved...—3.1 Motor eff. path. impaired.....—5.5
9 M. L.	11/16/39: Agitated; combative; apprehensive; oriented; evasive. No insight; occasional silly behavior	12/27/39: Oriented; less evasive. Better touch with reality; better insight; more emotional stability	10/21/39: Reactions resemble those of a nonproductive paranoid schizophrenic person. Labile mood. Judgment and intellect much impaired	12/17/39: Behavior became balanced; rapport became rather steady. Delusions disappeared; judgment and intellect improved significantly	General mental eff. very poor.....—2.7 Recent memory eff. fair.....—0.3 Remote memory eff. path. poor.....—5.4 Motor eff. poor.....—1.5	General mental eff. much improved.....—0.4 Recent memory eff. very good.....+1.0 Remote memory eff. much improved...—1.9 Motor eff. excellent.....+1.5
10 J. McA.	10/19/39: Agitation; blocking; delusions of grandeur; slight depression. Evasive, oriented. Fabricates source of infection	1/18/40: Less blocked; euphoric; oriented. Less insight; disconnected thinking; grandiose delusions	10/13/39: Strong "organic" indications;§ devastated picture with features of blocking and lack of affective responsiveness	1/24/40: Persistence of "organic" indications, but less blocking and appearance of some rapport, which only accentuates the intellectual deterioration	General mental eff. path. poor.....—5.8 Recent memory eff. very poor.....—4.3 Remote memory eff. very poor.....—3.1 Motor eff. path. poor.....—5.7	General mental eff. path. poor.....—5.2 Recent memory eff. very poor.....—3.9 Remote memory eff. very poor.....—3.3 Motor eff. path. poor.....—5.9
11 R. N.	10/19/39: Agitated; confused; disoriented. Delusions of grandeur; no insight; poor recent memory with rich confabulations. Fabricates source of infection	2/2/40: No essential change. Able to help some with ward work	9/22/39: Schizophrenic-like test reactions; no touch with reality. Disorientation; extremely low level of intellectual functioning. Very delusional	2/15/40: Disappearance of schizophrenic-like delusional picture, leaving only the devastation and emptiness of "organic" deterioration. Intellectual functioning unchanged	General mental eff. path. poor.....—10.0 Recent memory eff. path. poor.....—8.7 Remote memory eff. path. poor.....—10.0 Motor eff. path. poor.....—7.7	General mental eff. path. poor.....—9.0 Recent memory eff. path. poor.....—8.0 Remote memory eff. path. poor.....—9.3 Motor eff. path. poor but improved....—6.0

TABLE 3.—*Summary of Psychiatric Evaluations and Results of Psychologic Tests—Continued*

Patient	Psychiatric Evaluations		Rorschach Evaluations *		Results of Babcock Deterioration Test †	
	Before Metrazol Treatment	After Metrazol Treatment	Before Metrazol Treatment	After Metrazol Treatment	Before Metrazol Treatment Score	After Metrazol Treatment Score
12 R. Z.	10/10/39: Inactive; evasive; negativistic; oriented. Paranoid delusions; no insight; blunting of emotions	1/2/40: No change. Only slightly more active and cooperative	10/8/39: Impaired judgment. Schizoid, shut-in person, with delusional ideas and negativism	12/23/39: Slightly less delusional and less negativistic, with impairment becoming more marked	General mental eff. path. poor.....—7.0 Recent memory eff. very poor.....—2.0 Remote memory eff. path. poor.....—8.7 Motor eff. very poor.....—3.2	General mental eff. path. poor.....—6.0 Recent memory eff. very poor.....—2.4 Remote memory eff. path. poor.....—6.7 Motor eff. very poor.....—4.0
13 P. O.	10/30/39: Very negativistic; disoriented. Catatonic-like rigidity; periods of severe anxiety and fear	1/22/40: Decreased fear and anxiety; slight euphoria; better insight. Communicative; less negativistic and rigid	Catatonic state prevented testing	Language difficulty and insufficient cooperation prevented testing	Catatonic state prevented testing	Language difficulty and insufficient cooperation prevented testing
14 H. K.	11/10/39: Grandiose delusions; repetitions; hallucinations; no insight; intellectual impairment. Euphoric; negativistic	1/31/40: Delusions less grandiose and bizarre. Otherwise no change	10/27/39: Manic-like; very confused. Presence of many "organic" indications	1/25/40: Patient refused to take the test	General mental eff. path. poor.....—6.1 Recent memory eff. very poor.....—3.4 Remote memory eff. path. poor.....—6.1 Motor eff. very poor.....—4.5	Patient refused to take test
15 E. G.	10/15/39: Very hyperactive; excited; obscene; very aggressive; disoriented. Flight of ideas; some insight	1/3/40: Oriented; cooperative on ward. Mild euphoria; insight; better emotional stability. Inhibitions weak	11/10/39: Manic-like reactions; overwhelming sexual preoccupation; a few signs of "organic" involvement. Delusional, aggressive, impulsive, negativistic	12/19/40: Improvement similar to that of manic patients. Delusions and overt aggressions disappeared. Sexual preoccupations decreased; "organic" indications increased; became stable on low level of intelligence	General mental eff. path. poor.....—6.7 Recent memory eff. path. poor.....—4.2 Remote memory eff. path. poor.....—4.9 Motor eff. path. poor.....—5.8	General mental eff. poor but improved.—2.3 Recent memory eff. poor but improved—2.5 Remote memory eff. very good.....+1.5 Motor eff. poor but much improved....—2.0
16 H. J.	10/23/39: Psychomotor hyperactivity; distractibility; no insight; grandiose delusions; transitory illusions. Combative; partially oriented	12/1/39: Oriented; slightly depressed and anxious. Loss of illusions and delusions; improved psychomotor control	10/13/39: Catatonic-like with paranoid features. Strong delusions and impulsive excitement. Numerous indications of "organic" involvement	12/6/39: Improvement followed pattern of paranoid patients; became stabilized on very low level of intellectual functioning, with increased bodily preoccupation and increased indications of "organic" involvement	General mental eff. path. poor.....—7.8 Recent memory eff. path. poor.....—4.0 Remote memory eff. path. poor.....—7.4 Motor eff. path. poor.....—5.5	General mental eff. poor but improved.—3.7 Recent memory eff. poor but improved—2.5 Remote memory eff. fair.....—0.5 Motor eff. weak but improved.....—1.5

* Beck, S. Z.: Introduction to the Rorschach Method: A Manual of Personality Study, Monograph 1, New York, American Orthopsychiatric Association, 1925. Robb, R. W.; Kovitz, B., and Rapaport, D.: Histamine in the Treatment of Psychosis: A Psychiatric and Objective Psychological Study, Am. J. Psychiat. **97**: 601-610, 1940.

† Babcock, H.: An Experiment in the Measurement of Mental Deterioration, Arch. Psychol. 1930, no. 117, p. 105. In this column, "eff." means "efficiency" and "path." "pathologically."

‡ Orbison, W. D.; Eisner, E., and Rapaport, D.: Psychiatric Implications of Rorschach Studies with Metrazol and Sodium Amytal, read at the meeting of the American Psychiatric Association, Cincinnati, May 23, 1940.

§ Rorschach studies in metrazol treatment (Orbison‡; Robb, Kovitz and Rapaport*) suggested that when improvement has occurred the change in results of the post-treatment test as compared with those of the pretreatment test follows specific patterns for different groups of psychoses.

to time and to have auditory hallucinations. A well fixed delusional system developed. Administration of metrazol was always resisted and resulted at first in transitory improvement in accessibility and insight. Later the patient became very stubborn, antagonistic and uncooperative. After repeated hyperpyrexia she again improved, but not sufficiently to warrant parole.

CASE 5.—I. C., aged 39, a housewife, on first admission, in February 1938, exhibited mutism, negativism and untidiness. After hyperpyrexia, she was paroled in May 1938, but suffered a relapse and was readmitted to the hospital in December 1938. Flight of ideas, euphoria and partial insight persisted until metrazol treatment was started. At first she became cooperative, more controlled and less euphoric and the grandiose delusions were suppressed; later in the course of treatment, however, the delusions reappeared, though in a better organized form. This state persisted for several weeks after metrazol treatment was stopped; then the delusions were again submerged. In spite of continued improvement and satisfactory adjustment to the ward routine, the patient has not yet been paroled, because of residual impairment of judgment.

CASE 10.—J. McA., aged 33, a truck driver, had manifested symptoms of tabes and some intellectual impairment for about one year prior to admission. Grandiose delusions and fabrications concerning the manner of syphilitic infection appeared one week after he had been told he had neurosyphilis. Hyperpyrexia resulted in temporary improvement. At the beginning of metrazol therapy he showed marked agitation, blocking, evasiveness and grandiose delusions. He was frequently excited and combative prior to an injection of metrazol, but toward the end of the series of treatments he was less tense, showed less blocking and evasiveness and became euphoric, with a new set of expansive and grandiose ideas. These persisted for several weeks and then gradually subsided, leaving merely evidences of intellectual impairment.

GROUP III.—The following case deserves special mention because of certain atypical features.

CASE 9.—In the case of M. L., aged 34, a housewife, a diagnosis of dementia paralytica had been made on the basis of the history and the clinical findings on admission, despite the failure to find changes in the spinal fluid diagnostic of syphilis, a result which was interpreted as due to fifteen months' intensive chemotherapy. She exhibited marked confusion, blocking, furtiveness and intellectual impairment. Neurologic examination revealed a Babinski sign on the right side. No improvement followed malaria treatment, the patient remaining agitated and combative, with fleeting periods of silliness. After the fourth convulsion she became cooperative and noncombative, conversed rationally and spontaneously and exhibited more stability. Unfortunately, the metrazol treatment had to be discontinued because of the activation of latent pulmonary tuberculosis. For ten weeks thereafter the patient maintained her improved status and then gradually relapsed.

GROUP IV.—In evaluating the results in the cases discussed thus far the possibility had to be considered that improvement might be due to the previous hyperpyrexia rather than to the metrazol convulsions, as improvement often does not appear for some weeks or months after termination of hyperpyrexia. In the following 4 cases, in which hyper-

pyrexia was not employed prior to the metrazol treatment, the effect of metrazol on the psychosis of dementia paralytica is more clearly demonstrated.

Case 16.—H. J., aged 32, a Works Progress Administration laborer, had been admitted in a markedly excited, combative state, with flight of ideas, euphoria, grandiose delusions, transitory illusions and only partial orientation. Hydrotherapy produced some diminution of his hyperactivity. After the third metrazol convulsion the patient became oriented and cooperative; he lost his flight of ideas and manifested a touch of depression. The grandiose delusions gradually subsided, and he acquired insight. After thirteen convulsions he was well in touch with reality and did excellent work, but manifested some anxious preoccupation concerning his illness and continued to exaggerate certain of his previous experiences. He was paroled after hyperpyrexia, which resulted in improved physical well-being and disappearance of the aforementioned residual symptoms.

Case 15.—E. G., aged 39, a housewife, had been admitted in an extremely hyperactive and excited state, with marked flight of ideas, obscenity, clouding of consciousness, disorientation and transitory delusions. The usual sedative measures failed to produce any change in three weeks. After two metrazol convulsions the hyperactivity diminished; after the fourth treatment she was cooperative, in better touch with reality, oriented and able to adjust to ward routine. At the conclusion of metrazol treatment she was much improved, although still mildly euphoric, somewhat uninhibited and anxious concerning her illness. This residue decreased after hyperpyrexia. She was paroled and has made a good adjustment.

Case 13.—P. O., a Polish laborer aged 42, single, who exhibited profound malnutrition was admitted in a catatonic state of rigidity, negativism, disorientation and incontinence, with periods of severe anxiety tension. Only an occasional word or phrase could be elicited. The day after admission lobar pneumonia developed, which was aborted by administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) within forty-eight hours. After the first few metrazol convulsions he lost much of his fearfulness. Later he acquired sphincter control, dressed and fed himself, became rather euphoric, began to identify people and responded hesitantly in monosyllables to conversation. After the eleventh convulsion a relapse was observed. On further treatment improvement like that previously noted occurred, he gained 28 pounds (12.7 Kg.), became anxious to help other patients and engaged in spontaneous conversation. Despite evidences of profound intellectual impairment, he showed good insight. No delusions were elicited. After subsequent malaria therapy he showed further improvement, manifesting more spontaneity, alertness and ability to work. This improvement has been maintained with favorable prospects for parole.

Case 14.—H. K., a Negress aged 51, a widow, on admission had hallucinations, euphoria, bizarre, grandiose delusions, negativism and sudden outbursts of anger, with absence of insight. Nineteen metrazol convulsions produced little change, except that her delusions were less fantastic and grandiose. Subsequent artificial hyperpyrexia and specific chemotherapy yielded only slightly improved adjustment to ward routine.

COMMENT

Several questions may be raised and answered tentatively on the basis of the material presented.

1. What is the nature of the psychosis of dementia paralytica?

The improvements with the use of metrazol, as previously described, may be interpreted as supporting the theories (Hollós and Ferenczi,[5] Schilder,[6] Van Ophuijsen and Katan [7]) that maintain that the psychosis of dementia paralytica is not a simple consequence of the organic damage usually present in cases of this disease, but is a psychologic response to the syphilitic damage, corruptive to the self esteem.[8]

2. Were the cases in which the patients responded favorably to metrazol true cases of the psychosis of dementia paralytica, or did they represent functional psychoses occurring coincidentally with neurosyphilis of dementia paralytica type, similar to the cases reported by Barrett,[9] Postle [10] and Rothschild [11]?

In only 2 of our 16 cases (1 and 9) did it appear necessary to inquire into the probability of coincidental occurrence of neurosyphilis with a functional psychosis. However, the clinical and psychologic investigation of these cases failed to corroborate this probability. It is noteworthy that the histories of patients with the psychosis of dementia paralytica generally tend to show a distinct relation of the psychotic symptoms to the adjustment of the patient prior to the onset of dementia paralytica (Osnato [12]). In other words, the neurosyphilitic damage appears to bring to the surface and to exaggerate personality maladjustments previously present.

3. What is the clinical significance of the improvements elicited in these cases by the metrazol shock treatment?

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5. Hollós, S., and Ferenczi, S.: Psychoanalysis and the Psychic Disorder of General Paresis, Nervous and Mental Disease Monograph 42, New York, Nervous and Mental Disease Publishing Company, 1925.

6. Schilder, P.: Studien zur Psychologie und Symptomatologie der progressiven Paralyse, Abhandl. a. d. Neurol., Psychiat. Psychol. u. i. Grenzgeb. **58**:1-176, 1930.

7. Van Ophuijsen, J. H. W.: Psychoanalysis of Organic Psychoses, in Psychoanalysis Today: Its Scope and Function, New York, Covici Friede, 1933, pp. 273-280. Katan, M.: Psychology of General Paresis, Abstract from Dutch Psychoanalytic Society, Internat. Ztschr. f. Psychoanal. **17**:301, 1931.

8. We have summarized these theories in another article (Kenyon, V. B.; Rapaport, D., and Lozoff, H.: Note on Metrazol in General Paresis, Psychiatry **4**: 165-176, 1941).

9. Barrett, A. M.: Syphilitic Psychoses Associated with Manic-Depressive Symptoms and Course, J. A. M. A. **67**:1639 (Dec. 2) 1916.

10. Postle, B.: Pattern Features and Constitutional Susceptibility, as Related to Organic Brain Disease, with Special Reference to General Paralysis, J. Nerv. & Ment. Dis. **89**:26, 1939.

11. Rothschild, D.: Dementia Paralytica Accompanied by Manic-Depressive and Schizophrenic Psychoses: Significance of Their Coexistence, Am. J. Psychiat. **96**: 1043, 1940.

12. Osnato, M.: Personality in Paresis, J. A. M. A. **70**:434 (Feb. 16) 1918.

The only positive conclusion which seems warranted on the basis of the results reported is that metrazol is of therapeutic benefit in some cases of the psychosis of dementia paralytica which is unresponsive to syphilitic treatment and in cases of wildly delusional patients with early neurosyphilis, in whom it appears to suppress rapidly the delusions and agitation, preparing them for hyperpyrexia treatment.

SUMMARY AND CONCLUSIONS

Metrazol treatment was administered to a group of 16 patients with the psychosis of dementia paralytica. Twelve of these patients had previously received hyperpyrexia; 4 had no such treatment. Of the group which had previously received hyperpyrexia, 2 were sufficiently improved to be subsequently paroled and to maintain, after a lapse of twelve months, adequate social adjustment. Three patients showed some degree of improvement for periods ranging from six weeks to six months. Three patients showed definite changes in the clinical picture; at first these changes were unfavorable, but in 2 cases they were followed by moderate but lasting improvement. The condition of the remaining 4 patients showed practically no change. Of the group of 4 patients who had received no previous hyperpyrexia, 2 showed striking improvement and were paroled after the subsequent administration of hyperpyrexia; 1 patient exhibited improvement to a limited degree, and the condition of 1 was not changed.

Tabulations of the results of clinical, laboratory and psychologic tests, as well as data concerning the metrazol convulsions, are presented and discussed.

The justification for and the practical applicability and the theoretic significance of the use of metrazol in the treatment of the psychosis of dementia paralytica are discussed. The following conclusions are drawn:

1. There appears to be no particular danger in inducing convulsions in patients with dementia paralytica.

2. Patients with dementia paralytica appear to react to metrazol in a way similar to that of patients with functional psychoses.

3. As the psychosis of dementia paralytica was found to react to metrazol in much the same way as do the functional psychoses, the result may be interpreted as supporting theories which maintain that the psychosis of dementia paralytica is a response of the psyche to the organic damage.

4. The use of shock therapy appears to be warranted in those cases of dementia paralytica in which the psychosis does not respond to the usual methods of hyperpyrexia. However, further studies are needed to determine its ultimate place in the therapeutic management of dementia paralytica.

DILANTIN HYPERPLASTIC GINGIVITIS

ITS TREATMENT AND PREVENTION

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The occurrence of "sore mouth" as a frequent complication in the treatment of epilepsy with dilantin sodium (sodium diphenylhydantoinate) was first reported by Kimball [1] in 1939. Of 152 patients under treatment for from two to eleven months, 57 per cent showed changes in the gingival tissue, varying from slight to extreme hyperplasia. The changes were not proportionate to the amount of dilantin sodium ingested or to the length of time the patient had been taking the drug. As the appearance of the gingival tissues suggested scurvy (all other signs, such as purpura and sore joints, were absent), the ascorbic acid content of the blood serum was determined in a number of cases. From these serum analyses Kimball concluded that the degree of hyperplasia directly paralleled the deficiency of ascorbic acid. That is, persons with the most marked hyperplasia showed the lowest level of ascorbic acid, which dropped to 0.1 mg. per hundred cubic centimeters in some cases. However, the administration of large doses of ascorbic acid (300 mg. daily by mouth) did not materially improve the gingivae.

Merritt and Putnam,[2] in their original report, dealing mostly with adults, cited a much lower incidence of gingival hyperplasia after treatment with dilantin sodium (4 per cent as compared with the 57 per cent reported by Kimball). The chief difference between the two groups was that of age. The study by Merritt and Putnam "showed no evidence of a deficiency of ascorbic acid."

Frankel,[3] dealing with a mixed group of children and adults (chiefly adults) stated that 62 per cent of his series showed hyperplasia of the gums. The degree of gingival involvement paralleled the dose of dilantin

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1. Kimball, O. P.: Treatment of Epilepsy with Sodium Diphenyl Hydantoinate, J. A. M. A. **112**:1244 (April) 1939.

2. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in Treatment of Convulsive Disorders, J. A. M. A. **111**:1068 (Sept. 17) 1938.

3. Frankel, S. I.: Dilantin Sodium in Treatment of Epilepsy, J. A. M. A. **114**:1320 (April 6) 1940.

sodium, while the ascorbic acid level of the blood decreased as the gums grew larger. A study of the table accompanying this report leaves doubt as to the justification for Frankel's conclusions.

Thoma,[4] in the report of a case, expressed agreement with Merritt and Putnam in their view that the gingival hyperplasia is not related to the vitamin C level in the blood.

Gruhzit,[5] after inducing scurvy experimentally in guinea pigs, found that large doses of dilantin sodium did not alter the course of the scurvy or interfere with the utilization of vitamin C or of vitamin B.

Lennox [6] supported Gruhzit in the opinion that vitamin C deficiency is not related to dilantin hyperplasia of the gingivae.

Our own views, based on clinical observation and histologic evidence cited herein, are in accord with the statement of Merritt and Putnam that hyperplasia of the gums resulting from use of dilantin sodium is not related to vitamin C deficiency.

The peculiar stimulating action of dilantin sodium on the gum tissues, while not serious enough to necessitate withdrawal of the drug, should if possible be controlled in its initial manifestations, so as to save the patient discomfort and possible loss of teeth. Many patients whose condition was previously unrecognized as dilantin gingivitis have come to our attention in the dental school. In addition, we have observed a large group of patients under treatment for epilepsy in the Vanderbilt clinic.

PRESENT INVESTIGATION

The present report deals with a study of the gums of patients from both these sources. All were taking dilantin sodium daily. The series consisted of 7 children between the ages of 9 and 13 years, inclusive, of whom 2 were boys, and 7 adults, 4 women and 3 men, whose ages ranged from 16 to 44. Three boys, aged 8, 13 and 17 years, respectively, whose seizures had been successfully controlled with phenobarbital, were included for comparison. (For details of treatment see table.)

The chief complaints in cases of this condition are: (1) bleeding gums; (2) enlargement of the gums, with an ugly appearance, and (3) difficulty in mastication.

In the absence of therapeusis, symptoms of dilantin gingivitis progress steadily from mild to intensely severe.

As proliferation progresses in cases of severe involvement, the teeth are moved out of their natural alinement (fig. 1) and the interseptal bone

4. Thoma, K. H.: Dilantin Hyperplasia of Gingivae, Am. J. Orthodontics **26**:394 (April) 1940.

5. Gruhzit, O. M.: Sodium Diphenyl Hydantoinate: Pharmacologic and Histopathologic Studies, Arch. Path. **28**:761 (Nov.) 1939.

6. Lennox, W. G.: The Pharmacopeia and the Physician: Drug Therapy of Epilepsy, J. A. M. A. **114**:1347 (April 6) 1940.

Case No.	Sex	Age (Years)	Petit Mal	Grand Mal	Age at Onset	Frequency of Seizures (Approximate)	Dilantin Sodium Medication (Capsules [0.1 Gm.] Daily	Seizures While Under Treatment with Dilantin Sodium	Degree of Gingival Involvement	Oral Hygiene	Comment
1	♀	25	+	..	14 yr.	4 a day	3 or 4 for 2 yr.	None	++	Good	Responded to surgical removal and local massage readily; gums normal
2	♀	44	..	+	Childhood and at 36 yr.	2 a month	3 or 4 for 9 mo.; 1 or 2 now	None	+++	Fair	Responded to surgical removal and local treatment; gums practically normal
3	♀	21	+	+	Infancy	3 a day, mild; 3 a month, severe	3 for 2 yr.	Slight improvement	++++	Poor	Patient unable to cooperate
4	♀	9	+	..	5 yr.	40 a day	3 for 1 yr.	No change	+++	Poor	Improved with local treatment
5	♀	9	+	..	4½ yr.	24 a day	3 for 6 mo.	Improved	++++	Poor	Upper gums treated locally, with improvement; lower gums untreated, grew worse; surgical removal followed by massage
6	♀	9	..	+	6½ yr.	Several daily	4 for 2 yr.	No change	++++	Poor	Surgical treatment alone did not prove lasting; sizable regrowth after 2 mo.
7	♂	9½	+	..	9 mo.	Several every few weeks	4 for 1½ yr.	Little improvement	++	Poor	
8	♀	13	..	+	5 yr.	Several a week	6 for 1½ yr.; 3 now	Improved	++	Fair	
9	♀	27	+	+	Infancy and at 20 yr.	15 a month, severe; 3 a day, mild	3 for 1½ yr.	No change	++	Fair	
10	♀	10½	..	+	2 yr. 4 mo.	1 a day	2 for 1½ yr.; 3 now	Improved	+++	Poor	Improved with local treatment
11	♂	12	..	+	7½ yr.	3 a week every 2 months	2 for 21 mo.; discontinued 7 wk.; resumed	Improved	++	Fair	Improved when dilantin sodium was discontinued; grew worse when dilantin was resumed
12	♂	31	..	+	23 yr.	2 a week	6 to 8 for 1 yr.	None	0	Good	Received prophylactic treatment and instruction in home care at time dilantin was started
13	♂	16	+	+	13 yr.	1 a week, severe; 6 a week, mild	4 for 2 yr.	None	+++	Fair to Poor	Marked improvement after 1 wk. of intensive home care
14	♂	28	..	+	.....	Occasional	2 for 1 yr.	Improved	+	Good	Under dentist's care
15	♂	8	..	+	4 yr.	2 a day	Phenobarbital, 1 gr. (0.065 Gm.) a day	None	0	Good	Under dental supervision for past 3 yr.
16	♂	17	+	+	14 yr.	Several a day	Phenobarbital, 1½ gr. (0.097 Gm.) a day	None	0	Good	Mouth clean
17	♂	13	+	..	4½ yr.	30 a day	Phenobarbital, 1½ gr. a day	None	0	Fair	Presence of accumulations on teeth; marginal gingivitis

* The cases summarized in this table are representative ones selected to show all types of experiences met with in the larger groups studied. Cases 15, 16 and 17 of petit or grand mal were controlled without resort to dilantin sodium. These cases illustrate the nonoccurrence of hyperplastic gingivitis in the absence of dilantin sodium. In cases 1 to 14, inclusive, treatment with dilantin sodium, in varying doses, was employed. Seven were adults and 7 children; 9 were females and 5 males. There is no correlation between the gingival condition and the severity of the symptoms, the duration of the disease, the mode of onset, the degree of improvement with dilantin medication or the amount of dilantin sodium ingested. There is a direct relation between the cleanliness of the oral tissues and the degree of gingival involvement.

may be resorbed (fig. 2), producing looseness and sometimes loss of the teeth. If extraction is resorted to, the gums return to their normal appearance without further treatment.

Other sedatives used in the control of epileptic seizures do not possess the stimulating action on the gums described here (table).

APPEARANCE OF TISSUE

Gross Changes.—In the early stage proliferation appears from the under surface of the free gingival margin of the interdental papilla. It

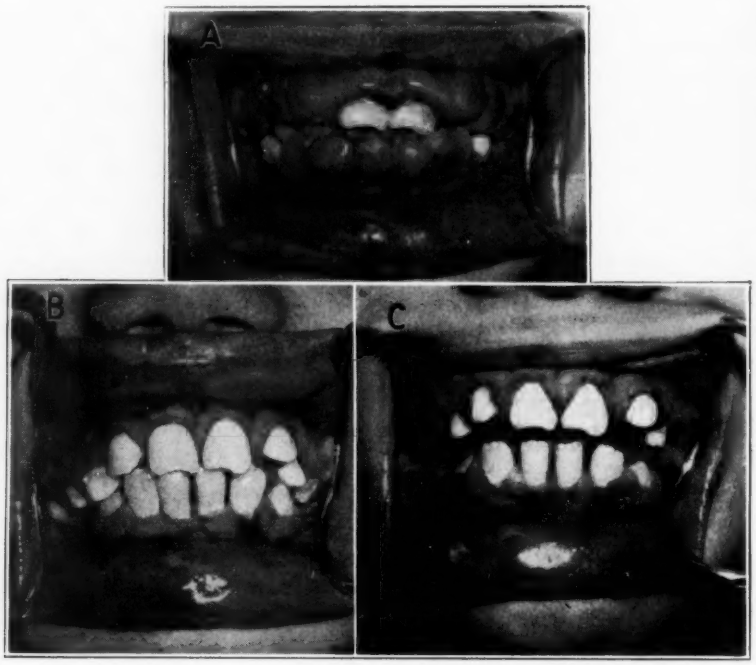

Fig. 1 (case 6, table).—A girl aged 9 years had taken 4 capsules of dilantin sodium (0.1 Gm. each) daily for two years; at present she is receiving 5 capsules daily. *A,* photograph taken May 15, 1940, showing thickening and downgrowth of the entire alveolar gingiva, with a tendency to bury the teeth. In this enlarged state of the gums, mastication becomes difficult and the esthetic problem becomes acute.

B, photograph taken on Oct. 12, 1940, after the surgical removal of hyperplastic portions of the gingiva.

C, photograph showing regrowth in twelve weeks after surgical removal, without further treatment. Note also the increased spacing of the teeth.

spreads along the margins, advancing toward the sulci, and the tissue resembles that frequently produced by chronic local irritation. At this

juncture the condition is familiar to dentists as gum polypi or a form of localized hypertrophic gingivitis. A similar proliferation is frequently seen during pregnancy in areas subject to chronic irritation.[7] The tissue is congested, shiny and friable, with a definite line of demarcation between it and the stippled portion of the gingiva (fig. 5 *A*). (Sometimes the aid of a magnifying glass is necessary to see the line of demarcation.)

As the proliferation increases the whole alveolar gingiva becomes thickened and extends crownward until, in some cases, it buries entirely one or more teeth (fig. 1 *A*). At this stage, mastication is difficult and often painful.

The growth process continues. The gingivae become hard and firm, eventually taking on the appearance of normal gingivae which are greatly enlarged. Finally, the picture is one of generalized fibromatosis.

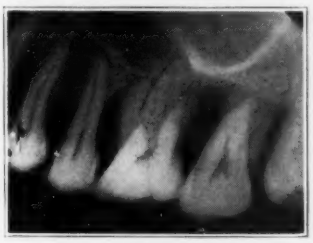

Fig. 2 (case 3, table).—The interseptal bone has been lost. The teeth in this area were loose, and toothache, due to the periodontitis, necessitated removal of the first and second molars. After the extractions the gums in this area returned to normal.

Microscopic Appearance.—Epithelium: The keratin layer is not much altered, although it appears somewhat thinner than usual. The epithelium shows proliferative change, evidenced by the greatly increased number of nuclei in the prickle and basal cell layers. The hyperchromatic nuclei take a deep stain and show an increased number of mitotic figures. There is some hydropic change. The epithelial proliferation is again accentuated by the downgrowth of the epithelial pegs fairly deep into the corium and by their pointing and frequent splitting.

In some sections epithelial whorls are seen (fig. 3). These may be due to the growth of the epithelial pegs and to their having been sectioned at right angles. However, a low degree of cornification can be seen in the center of the whorls.

7. Ziskin, D. E.; Blackberg, S. N., and Stout, A. P.: Gingivae During Pregnancy: Experimental Study and Histopathological Interpretation, Surg., Gynec. & Obst. **57**:719 (Dec.) 1933.

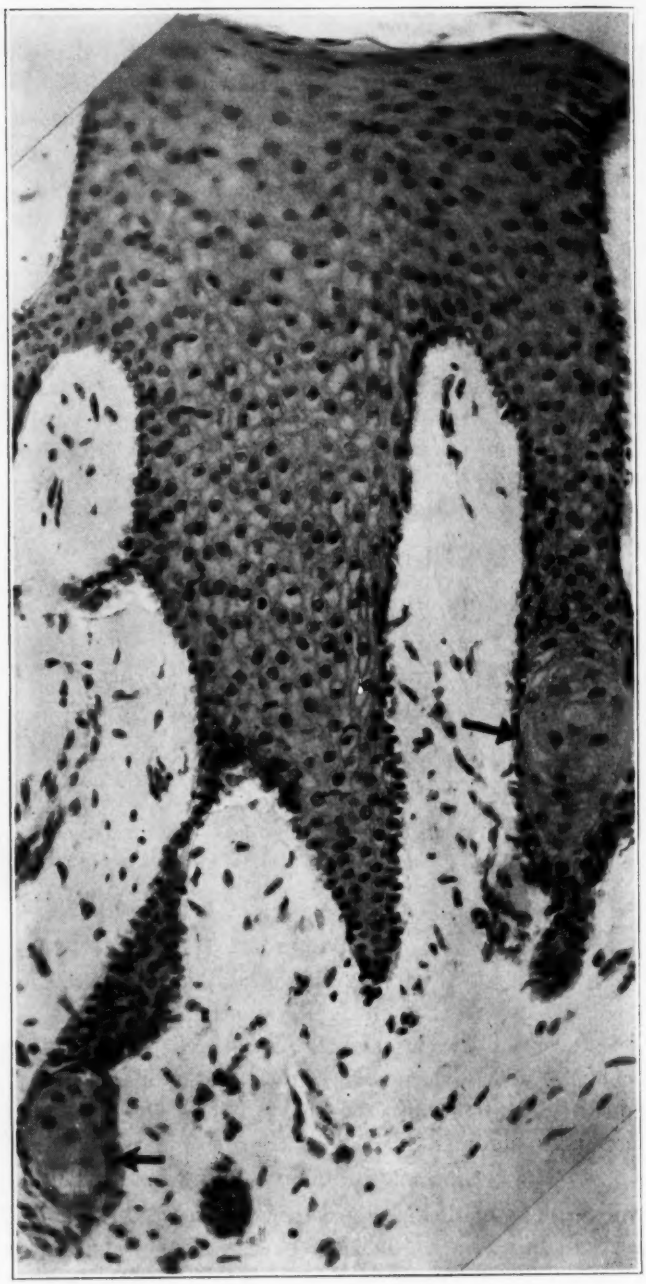

Fig. 3 (case 4, table).—A girl aged 9 years had been taking 3 capsules of dilantin sodium daily for one year. The alveolar gingiva shows epithelial whorls in the strandlike projections of the epithelium, which are probably due to the growth of the epithelial pegs and their having been sectioned at right angles. A low degree of cornification is seen in the center. Magnification 280.

Connective Tissues: The proliferation of the corium is even more marked than that of the epithelium and seemingly accounts for most of the gingival enlargement. Many large young fibroblasts in an apparent state of hyperactivity are seen throughout the interdental and alveolar portions of the stroma. There are masses of inflammatory exudate,

Fig. 4 (case 4, table).—Alveolar gingiva showing the tip, or crest, of an interdental papilla (upper left central), from a biopsy specimen. Note (*A*) the keratin layer, which is somewhat thinner than usual; (*B*) general hyperplasia of the epithelium; (*C*) downgrowth of epithelial pegs, with pointing and frequent splitting; (*D*) papillary layer close to the outer surface of the epithelium; (*E*) cellular connective tissue, rich in young hyperchromatic fibroblasts; (*F*) increased vascularity; (*G*) dense masses of inflammatory cells, many of which are perivascular, and (*H*) epithelium covering an outgrowth of connective tissue. Magnification 60.

chiefly perivascular and composed mainly of round cells, with some plasma cells and a few polymorphonuclears. This inflammatory reaction, although fairly prominent in the alveolar corium, is especially conspicuous at the crest of the interdental papillae. There is an increase in the size and number of blood vessels and lymph channels. Endothelial proliferation resulting in the formation of new capillaries is seen in the periosteal portion of the corium in some sections. Edema is a prominent feature in some cases and not in others. The papillae of the corium lie abnormally close to the outer surface of the epithelium and usually contain groups of young fibroblasts.

The proliferation of the connective tissue extending over the surfaces of the teeth becomes covered with epithelium, probably by direct extension of the epithelial covering (fig. 4).

SCURVY AND DILANTIN HYPERPLASIAS: A DIFFERENTIAL APPRAISAL

The resemblance of dilantin hyperplasia of the gums to the hypertrophy seen in scurvy is a superficial one. At certain stages in the development of the two conditions the clinical manifestations appear to be the same. However, it must be noted that the hypertrophy occurring in scurvy is caused by swelling and not by hyperplasia, as it is in dilantin gingivitis. Other indications of scurvy are pain, marginal necrosis of the gums, occasional petechial hemorrhage and invariable loosening of the teeth. These signs are absent in dilantin hyperplasia, as are such constitutional symptoms as purpura and sore joints.

The microscopic differences between the two conditions are even more emphatic. The outstanding features of scurvy are: (1) failure of the cells of the supporting connective tissues to form or maintain intercellular substances; (2) failure of capillary formation, due to inability of endothelial cells to form cement substance; (3) prevention or suspension of the proper maturation of structural embryonic connective tissue; (4) impeded ability to form collagen, causing a reduced immunologic response on the part of the gums, which permits marked inflammation and surface ulcerations, and (5) atrophic changes in the periodontium, resulting in its inability to support the teeth, with consequent loosening.[8]

8. Boyle, P.: Effect of Ascorbic Acid Deficiency on Enamel Formation in Teeth of Guinea Pigs, Am. J. Path. **14**:843 (Nov.) 1938. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1**:1 (Jan.) 1926. Menkin, V.; Wolbach, S. B., and Menkin, M. F.: Formation of Intercellular Substances by Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, Am. J. Path. **10**:569 (Sept.) 1934. Rinehart, J. F., and Mettier, S. R.: Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection, with Notes on Similarity of Lesions to Those of Rheumatic Fever, ibid. **10**:61 (Jan.) 1934. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 271.

The outstanding features of dilantin stimulation are increased collagen formation and an increase in capillary formation.

ETIOLOGY

In the table it will be seen that the medical diagnosis, the severity of the epileptic symptoms, the amount of daily medication and the beneficial results of the therapy have no bearing on the degree of severity of the dilantin gingivitis. While the length of treatment with dilantin sodium is seemingly a factor in that the longer a patient is treated the more pronounced is the enlargment of the gums, some patients receiving dilantin sodium over a long period show less involvement than others who ingest the drug for a shorter period.

The mucous membranes (other than the alveolar gingiva) and the edentulous parts show no noticeable change.

The most severely affected areas seem to be those which are in contact with irritants, such as tartar or other accumulated substances or ill-fitting dental restorations with overhanging margins. The same mouth may disclose both normal-appearing and grossly involved tissue. In extreme instances the entire alveolar gingiva is affected.

Patients with little or no hyperplasia of the gums gave their mouths excellent hygienic care, while those with gross lesions showed careless application of the toothbrush. This factor was especially noticeable in children. In investigating the toothbrush habits of both children and adults, it was seen that in the same mouth areas receiving the best care were not involved to the same degree as were other parts where signs of negligence were present.

These factors lead to the hypothesis that because of the stasis produced in the terminal capillary circulation of the gums by local inflammation, the action of dilantin sodium in producing tissue hyperplasia is made possible. The exact method by which the drug exerts its action remains to be determined.

TREATMENT

Surgical removal of the hyperplastic tissue was found to be ineffectual (fig. 1) because of the rapid regrowth. Therapy consisting of vigorous massage of the interdental papillae or of surgical intervention followed by massage proved more successful. The following case (case 1 in table) is descriptive of the procedure.

A woman aged 26, single, had been treated with dilantin sodium for two years. The present dose was 3 or 4 capsules (0.1 Gm. each) a day. The patient was unusually intelligent and cooperative.

History.—Enlargement of the gums was obvious within six months after ingestion of the drug was begun. The dentist who was consulted, without recognizing the pathosis, instituted routine prophylactic care, with some resultant improvement.

Considerable enlargement was present (fig. 5 *A*) when the case came to our attention. Therapeutic measures were instituted as follows: In the upper jaw vigorous massage was employed, consisting of the interdental method of brushing the teeth plus the use of a rubber interdental stimulator or a round toothpick. In the lower jaw the proliferations were removed surgically, followed by massage

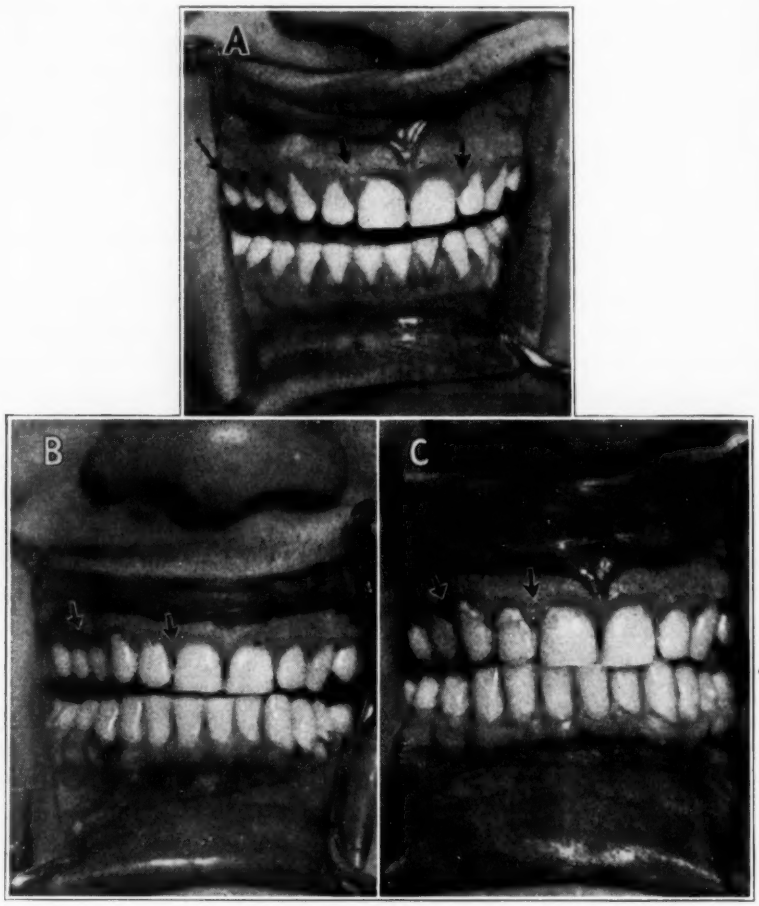

Fig. 5 (case 1, table).—A woman aged 25 years had taken 3 to 4 capsules of dilantin sodium daily for two years. *A*, photograph taken Oct. 11, 1940, before dental treatment was begun. Arrows point to the line of demarcation between the normal and the hyperplastic gingiva.

B, photograph taken November 11, three weeks after local interdental stimulation of the upper gum was begun and after surgical treatment of the lower gum. Note that the upper gum has returned to normal.

C, photograph taken Feb. 17, 1941, fourteen weeks after that in *B*. Local interdental stimulation had been continued in all but the upper right quadrant. Note the return of dilantin hyperplasia in this area, the rest of mouth remaining normal. Arrows point to the line of demarcation between the same areas as those in *A* and *B*.

as soon as the gums were sufficiently healed. The method of massage was that already described. Treatment of the upper and the lower gingiva was started at the same time.

The upper gingiva returned to normal in three weeks. The lower gingiva also healed, but much more slowly (fig. 5 *B*). After the entire mouth had been restored to an apparently healthy condition, the massage was continued as before in all but the upper right quadrant of the mouth. Here the patient was instructed to discontinue home care. Within two weeks the dilantin gingivitis returned in this area. Figure 5 *C* is a photograph taken fourteen weeks later. The rest of the mouth remained normal with continuous home care.

The progress of this patient suggests that the early prophylactic care given her by her dentist may have prevented the extreme enlargement seen in untreated persons.

SUMMARY AND CONCLUSIONS

The important changes produced by dilantin sodium are marked hyperplasia of both the connective tissue and the epithelium, the hyperplasia being most pronounced in the corium. The connective tissue proliferates, growing out from the under surface of the free margin of the gum and covering wholly or in part the crown of the tooth. The proliferative tissue becomes covered with epithelium. This new tissue is hard and firm and takes on the appearance of normal gingiva which is greatly enlarged.

This hyperplasia has but slight resemblance to that of scurvy and is not significantly altered by the administration of ascorbic acid. Microscopically the two diseases are entirely dissimilar.

Surgical removal of the hypertrophied tissue is inadequate. Surgical intervention, plus massage and hygienic care, is advisable in instances in which the growth of the gums has advanced to such an extent that prophylactic measures cannot be employed without first reducing the size of the gums.

The best response is obtained by routine home care, including interdental massage.

Because of the apparent therapeutic value of this method in minimizing, and possibly preventing, the condition, gingival treatment should be begun early, preferably when dilantin therapy is started. Medication with the drug need not be discontinued because of the gingival hyperplasia.

REMOVAL OF TUMOR ARISING ANTERIOR TO THE MEDULLA

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SYRACUSE, N. Y.

The late Harvey Cushing [1] considered meningiomas with dural attachment in the region of the foramen magnum as either craniospinal or spinocranial. The former arise from the basilar groove of the occipital bone, thence project downward into the spinal canal and lie anterior to the medulla and the upper part of the spinal cord. The latter arise below the foramen, extend upward and lie posterior or posterolateral to the spinal cord.

Cushing and Eisenhardt [1] referred to several craniospinal tumors, in all instances of which there was a fatal issue. They then stated (page 180): "Whether a meningioma arising from the basilar groove which must be overlain and concealed by a posteriorly dislodged medulla and its emerging nerves could be safely exposed and surgically enucleated must be left for further experience to determine." A current search of the literature revealed but 1 instance [2] in which this operation had been successfully performed. The present case is believed to be the second to be reported in which this procedure was carried out with apparent complete removal of the tumor and recovery of the patient.

REPORT OF A CASE

H. B., a 48 year old brick setter, was referred on July 30, 1940 by Dr. W. C. Harding because of suboccipital headache and weakness of the right extremities. The family and past histories were irrelevant. The present illness began in January 1940 with the onset of suboccipital and nuchal "lameness" as well as transitory numbness of the right hand and general fatigability. The suboccipital discomfort, which increased at bedtime and frequently awakened the patient in the early morning hours, progressed through the spring. In mid-June slowness and weakness of the right hand and numbness of the left hand and forearm were first observed. The weakness of the right hand progressed slowly for two weeks and thereafter remained stationary. Toward the end of June the patient started to limp on the right side. From early June he noticed that when taking a hot bath, he did not feel the heat so much on the left side of the body as on the right. Since July 25

From the Syracuse University College of Medicine and the University Hospital.

1. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C. Thomas, Publisher, 1938, pp. 87-91 and 169-180.

2. Voss, O.: Basale Meningeome der hinteren Schädelgrube, Arch. f. klin. Chir. **189**:494-497, 1937.

there had been a continuous "tight feeling" in the epigastrium. The fatigability, which had been present for six months, became worse at this time.

General physical examination yielded no noteworthy abnormalities. A summary of the significant features of the neurologic examination performed on July 30, 1940 follows: The patient walked with a slight limp on the right. The tip and the lateral border of the sole of the right shoe showed excessive wear. The right side of the body showed weakness, which included the trapezius muscle, the side of the neck and both limbs. There was atrophy of the muscles of the right upper limb, most marked in the interossei. The muscles on the left side of the body were normal. There were moderate incoordination and adiadokokinesis of the right limbs, but not more than could be accounted for by weakness. Sensation of light touch was normal throughout. There were analgesia and thermanesthesia below the third cervical dermatome on the left side. Vibratory sensation was markedly diminished in both lower limbs and moderately decreased in both upper limbs, more so on the right. Joint sensation was slightly diminished in the right upper limb, but was normal in the left upper and both lower limbs. There was normal stereognosis in the hands. All deep tendon reflexes were increased and equal on the two sides. The abdominal reflexes were absent, but the cremasteric reflexes were normal. There was transitory ankle clonus, more persistent on the right than on the left. Babinski's sign was present on the right but was absent on the left. There was tenderness on percussion over the suboccipital region, but not over the spinous processes of the vertebrae.

The working diagnosis was involvement of the uppermost cervical part of the spinal cord on the right side (Brown-Séquard syndrome, with a lesion in the region of the foramen magnum). Roentgenograms of the skull and the cervical portion of the spine, with special reference to the foramen magnum, as well as the plates of the chest, showed nothing significant. Routine analyses of the blood and urine gave normal results. Lumbar puncture, performed on August 6, yielded clear, slightly yellow spinal fluid, under a pressure of 7 cm. of water. Despite prompt rise and fall in pressure on transitory abdominal compression and on coughing, there was no response either to bilateral manual jugular compression or to pressure applied to the neck with the cuff of a sphygmomanometer. There was, therefore, complete spinal subarachnoid block. After 10 cc. of fluid was removed the final pressure was 2.5 cm. The fluid contained 333 mg. of total protein per hundred cubic centimeters but no leukocytes.

Neurologic reexamination on the day after the lumbar puncture revealed that the analgesia on the left side now included the third cervical dermatome. Passive flexion of the head to either side was slightly painful, but was more limited on the right than on the left. Although there was no further alteration of strength in the right limbs immediately after the puncture, hemiplegia on that side had progressed markedly six days later. There was no additional change in sensation.

Operation.—Operation was performed August 15, with the preoperative diagnosis of tumor in the high cervical portion of the spinal cord, possibly extending into the foramen magnum. Anesthesia was obtained by the administration of avertin with amylene hydrate rectally and procaine hydrochloride locally, supplemented by intramuscular injections of small amounts of codeine and intravenous injections of sodium amytal for restlessness toward the end of the procedure, which lasted three and three-quarters hours. A transfusion of 350 cc. of blood was given as a routine measure to prevent shock.

With the patient in the prone position, a primary midline nuchal incision, extending from the spinous process of the fourth cervical vertebra to the external

occipital protuberance of the skull, was made. The right hemilamina of the second cervical vertebra, part of that of the third, the posterior arch of the atlas and a small bit of occipital bone forming the wall of the foramen magnum on the right side near the midline were removed. There was thus exposed the pulsating dura over the uppermost part of the spinal cord and over the posterior fossa on the right side. The dura was then opened to reveal the cervical portion of the cord and its junction with the medulla oblongata. One could also see the uppermost cervical roots on the right side and the spinal part of the right spinal accessory nerve, immediately beneath which was a tumor, which seemed grayish red under the arachnoid. A spinal puncture needle was then inserted into the tumor to see whether it was a cyst or an aneurysm. No fluid was obtained. After the arachnoid over the cisterna magna was opened the right cerebellar tonsil appeared. Then the right second cervical nerve, which crossed the tumor, was cut after silver clips were applied. Tenuous blood vessels passing from the cord anteriorly around

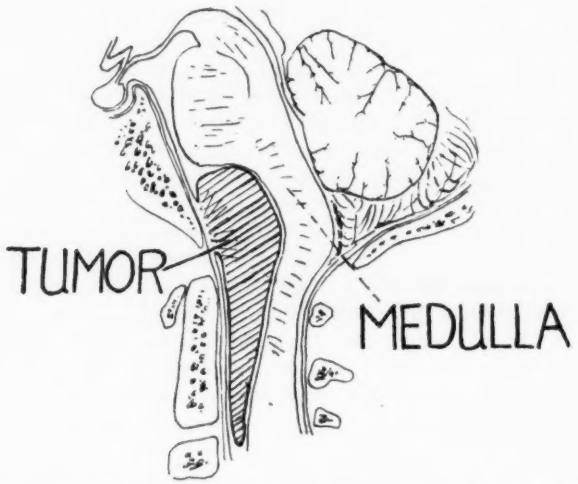


Fig. 1.—Relations of the tumor to neural and osseous structures (modified from Cushing and Eisenhardt [1]).

the tumor were electrocoagulated and cut. At first it was difficult to separate the cord and the tumor because of the arachnoidal adhesions, but after the start the separation was easy. The tumor was nodular and roughly cylindric and measured 4.5 cm. in length and 2 cm. in diameter. It passed ventral to the spinal cord and medulla and displaced these structures posteriorly and to the left side. It extended from the third cervical vertebra to about 2 cm. above the rim of the foramen magnum (fig. 1). The tumor had to be removed piecemeal with pituitary forceps in order to avoid too much traction on the medulla and the spinal cord. It was moderately vascular. After the blood was cleared away, the dura anterior to the cord and medulla was found to be smooth everywhere except for a bleeding, roughened area, 1 cm. in diameter, in the midline at the basilar groove of the occipital bone, that is, the anterior border of the foramen magnum. This area, which obviously represented the pedicle of the tumor, was very near the right vertebral artery, the entire intracranial portion of which was in the field of operation and which, surprisingly, did not give rise to a descending branch. Dr. George

Reifenstein came to the operating room and made a biopsy of fresh tissue, which showed characteristic nuclei in whorls, indicative of meningioma. Subsequent examination by Dr. J. H. Ferguson confirmed this diagnosis. While attempting to remove tissue from the pedicle, I encountered brisk arterial hemorrhage from its base. After the hemorrhage was controlled with hemostats, I coagulated the area so that it was charred, both to stop the bleeding and to destroy tumor cells which presumably were embedded in the meninges at this point. Therefore it may be assumed that the tumor was completely removed (fig. 2). At the end of the operation a plain Penrose drain was left in the subarachnoid space. The dura was closed with a continuous silk suture, the muscles and ligaments with interrupted wire sutures and the skin with interrupted silk sutures. At no time was there any marked alteration in blood pressure, breathing or pulse rate. In brief,

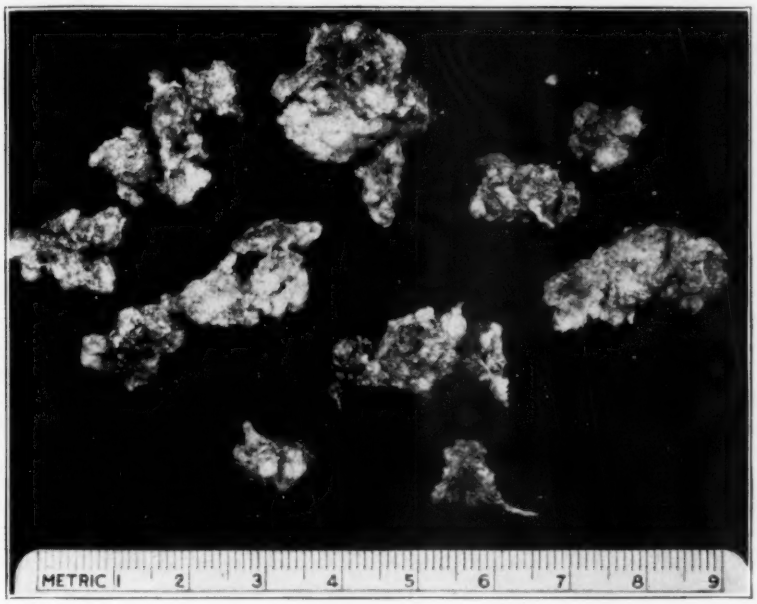


Fig. 2.—Tumor removed at operation.

the operative procedure consisted of a right cervical hemilaminectomy combined with a small suboccipital craniectomy and complete removal of a craniospinal tumor.

Postoperative Course.—The convalescence was gratifying. A few hours after operation the patient swallowed normally, and after a few more hours he voided normally. Spinal fluid first was bloody but later became clear, and there was no evidence of spinal subarachnoid block. The wound healed by primary intention, and all sutures were removed on the ninth postoperative day.

Neurologic changes during the convalescence were marked first by paralysis of the right upper limb, which lasted thirty-six hours. There was also analgesia, but not anesthesia, in the area of skin subserved by all three divisions of the right trigeminal nerve. The corneal reflex and corneal sensation were unimpaired. The new area of analgesia was considered the result of traction on the descending root of the trigeminal nerve. For the first week there was also extreme incoordi-

nation in the finger to nose test on the right side; this was attributed to traction on the restiform body during operation. At the time of dismissal from the hospital, on the twentieth postoperative day, the patient had good movements of the neck, a mild Horner syndrome on the right side, persistent analgesia in the cutaneous area subserved by the right trigeminal nerve and the Brown-Séquard syndrome of which he originally complained. However, the hemiplegia had improved considerably from the condition immediately before operation, and the patient walked with but a slight limp.

He reported on September 21, five weeks after operation. He had begun to shave himself and could carry a glass of fluid to his mouth with his right hand. He was able to dress himself. Examination disclosed persistence of the Horner syndrome on the right side, diminution in the degree of analgesia of the right side of the face and normal pain sensation in the left third and fourth cervical dermatomes. There was analgesia below this level on the left side. Babinski's sign was no longer present. At this time atrophy of the sternocleidomastoid, trapezius and deep neck muscles was more pronounced on the right. The patient's gait was almost normal, and the strength in his hand was improving. On October 18, two months after operation, he was able to walk on his toes. He said he was shaving himself with his right hand, and his general health was excellent. He had slight return of pain sensation along the right side of the nose and lips, as well as in the left hand. There was a fair grip in the right hand, but paralysis of the right serratus anterior muscle and other rotators of the scapula persisted. There was considerable return in strength of the muscles of the neck, isasmuch as he could bend his head to either side with moderate strength. In bringing his right index finger to his nose there was minimal incoordination.

On April 7, 1941, approximately eight months after operation, the patient looked and felt well. His only complaints were slight stiffness of the right shoulder on abducting the arm and occasional stiffness in the back of the neck on turning his head rapidly. Both these conditions were improving. He had been doing light jobs without difficulty and was ready to undertake his regular occupation of brick setting as soon as a job was available. Examination revealed almost complete functional recovery. There was hypalgesia of minimal degree in the upper two thirds of the right side of the face and on the left side of the body below the neck. Analgesia was present only over the anterior aspect of the lower part of the left leg, in its lower half. There were atrophy and weakness only of the right trapezius and sternocleidomastoid muscles and of the muscles of the back of the neck on the right side. No evidence of Horner's syndrome or signs of involvement of the pyramidal tract were noted.

On May 22 the patient reported to his regular work as a brick layer. On August 8 he wrote that he had lost no time from his work and that he was gaining weight and feeling fine.

SUMMARY

There is reported a second case of apparently complete, successful removal of a meningioma which arose from the anterior rim of the foramen magnum and which had displaced the medulla and spinal cord backward.

Obituaries

OTFRID FOERSTER
1873–1941

Ich, Otfried [1] Foerster, Sohn des Geheimrath Prof. Dr. Foerster, bin geboren zu Breslau den 9. November 1873. Nachdem ich die Vorschule des Gymnasiums zu Rostock und Kiel, das Gymnasium zu Kiel und das Maria-Magdalenen-Gymnasium zu Breslau besucht, bestand ich im März 1892 das Abiturientenexamen. Ich widmete mich darauf vom S. S. 1892 bis S. S. 1896 dem Studium der Medicin auf den Universitäten Freiburg i/Br., Kiel und Breslau. Des Tentamen physicum legte ich in Kiel im März 1894 ab, das medicinische Staatsexamen in Breslau während des Winter-Semesters 1896/97, das Tentamen rigorosum ebenda im März 1897.

The foregoing quotation is the *Lebenslauf* written by Foerster at the end of his doctor's thesis in 1897, and contains the early biographic facts. His father was professor of archeology, and in the course of university appointments and progress his son was taken to Rostock when he was 2 years old, then to Kiel when he was 8 years old and back to Breslau when he was 17. This early cosmopolitan trend continued and characterized the man; it was striking in so remote a city as Breslau. In his preparation for the university he emphasized the humanities and laid the foundation for a very broad, cultural development and an art in expression, written, spoken or pantomime, which perhaps no contemporary scientist possessed. His teachers were very sad when he did not become a philologist; his promise must have been great if his ability to express himself in languages other than German was any criterion. His addresses in French or English were exquisite; interjections of Greek and Latin were part of his natural expression in lectures and in writing. The collecting of stones and of butterflies was his earliest avocation, which later turned to music and to the theater; he played the flute with great finish and was very active and reputedly excellent in theatricals.

When he entered the university at Freiburg he had not yet decided whether the natural sciences or medicine would be his career. At this stage the preparation was the same for both. In the following year he decided to enter medicine and went to Kiel, where he took special interest in the anatomy of the brain and worked with Walter Flemming. After two years at Kiel, he returned to Breslau in 1894, where he passed the clinical semesters and was immediately recognized for his great abilities.

After having completed his doctor's thesis in 1897, he was sent by Wernicke to work with Frenkel at Heiden, in Switzerland, for the next

1. The "e" disappeared about 1900.

two summers, while he spent the winter semesters in Paris with Dejerine. Thus, he entered neurology directly he obtained his medical degree, and almost simultaneously he started to investigate movement and sensation, working in the fertile field of tabes.

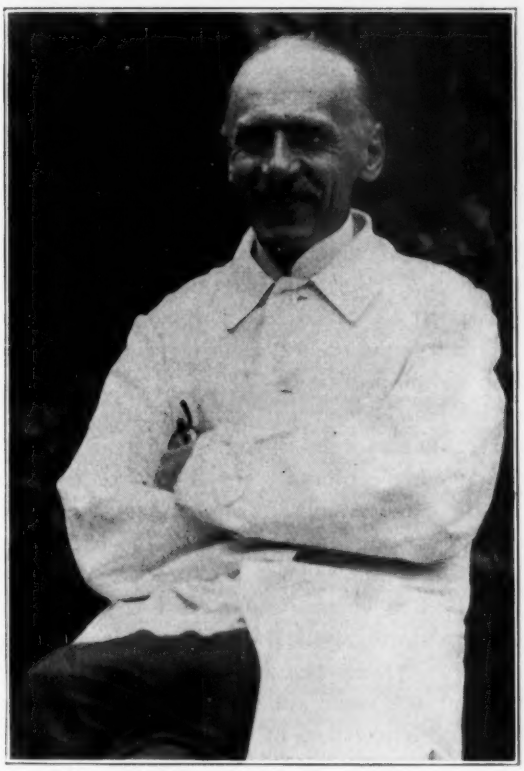
In 1899 he returned to Breslau, where he lived until his death. He became assistant to Wernicke and made such a brilliant success with neurologic therapy that Wernicke, a man of few words, said, "Ich habe jetzt einen Assistenten, der macht die Lahmen gehen und die Blinden sehen." During these early years he set his lifelong course—analysis of pathologic physiology coordinated with anatomy—toward his goal, practical therapy. Hughlings Jackson and Sherrington were his guiding stars. He had the inclination and the capacity to formulate his own theories from personal observations. This characterized his work, in which there was only rare reference to the literature. His papers were written boldly, without concern for precedence or reputation.

He became *Privat-Dozent für Nervenheilkunde* in 1903, when he completed his *Habilitationsarbeit* under Wernicke. He then entered practice, in which he was extremely successful. He was called into consultation over the whole of Europe, and his patients came from the entire world. The most famous of these was probably Lenin, whom he attended for a few years and whose brain he removed for study by Vogt. He was kept in Russia at the insistence of the German Foreign Office, for at that time Germany and Russia had close diplomatic relations, and it has been said that when Poland was threatening war on Silesia, Foerster was responsible for Russia's warning to Poland. Thus his native province remained undisturbed. He spent much of the time while in Russia preparing his monograph, "Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände."

From his early days at the Allerheiligen Hospital he had carried on his investigations in the cellar and had personally subsidized his work. He bought apparatus of all kinds and continued to bear the expense of all his experimentation until the Rockefeller Foundation gave him support, about 1930. And indeed when the new institute was built he installed all his scientific property in it and contributed it for further work. He did the same with his library. Even after 1921, when his service was moved to another of the Breslau municipal hospitals, the Wenzel Hanke Krankenhaus, with its generous accommodations for about 200 patients, the physiologic laboratory was again in the cellar and the pathologic laboratory was formed by a partition in one of the hallways between the wards. The new institute finally had most spacious arrangements of all kinds, and only then did he have reasonable room for his assistants and his pupils.

His scientific activity will probably always be considered as abstract investigation on the human nervous system, and although this may

appear to be so in one light, it should not be forgotten that his observations were by-products of therapeutic efforts. One need only recall that his earliest physiologic studies of the central nervous system, those having to do with coordination and associated movements, had practical therapeutic application throughout his whole life. He first wrote on exercise therapy at the beginning of the century, and one of the last sections which he wrote for the recent "Handbuch der Neurologie" was entitled "Uebungstherapie."



OTFRID FOERSTER
1873–1941

It is singular that both Otfrid Foerster and Harvey Cushing, who established separate neurosurgical schools, should both have written their first medical papers on typhoid fever. Foerster's development was quite different from that of Cushing, who began as a surgeon and, in the course of time, acquired a wide neurologic knowledge. Foerster's preparation was the reverse. He was first and foremost a neurologist, one who stood out among his contemporaries as did Cushing in surgery among his. Foerster's surgical preparation came very late, and he did not enter surgery until the war, when he was already in his fifth decade.

It has been said that he undertook surgery because of war conditions, but his own explanation was that he was unable to get surgeons to do exactly what he wished. Mikulicz, one of his teachers, had urged him to become a surgeon because of natural dexterity, but apparently the mental gymnastics of neurology had a greater attraction than the physical manipulations of surgery until he found the latter important, indeed essential, to accomplish his purposes.

It was quite obvious to one watching Foerster operate that he did not grow up in surgery. The first glance at his operating room arrangements and his technic was surprising. Everything seemed to be unusual and unsurgical. If one were to imagine a cerebral operation carried out without making a bone flap (for he rongeured away the bone over the area to be exposed), cerebral hemostasis without silver clips or electrosurgical methods and maintenance of a clear field without suction apparatus, one might readily imagine that one were witnessing surgery of the brain in the Middle Ages. It was indeed astounding that his results could have been compared favorably with those of most other European neurosurgical clinics in his time. But when one saw him working on the spinal cord and the peripheral nerves, one could say without hesitation that more delicate surgery could not have been done. In these fields he had no peers.

It is difficult to point to any particular phase of neurology in which Foerster was preeminent, for he ranked so high in all his undertakings that none stood above the others. He is now probably better known for his work on the cerebral cortex than for his other accomplishments because it is within the immediate vision of the present. At the turn of the century he was renowned for his success with exercise therapy. Within a decade he had become famous for division of the posterior roots in treating spastic paralysis. This procedure was then known as Foerster's operation. It was soon applied for relief of the gastric crises of tabes. At about the same time, in 1909, he described a clinical picture in children, characterized by marked hypotonia in the reclining position and by hypertonia in the vertical position. This was called the syndrome of Foerster. As early as 1912 he had his associate, the surgeon Tietze, divide the anterolateral tract for the relief of pain, this being done independently of the work of Spiller and Martin of the year before. Already in 1912 he used biopsy specimens taken by needle puncture for the histologic study of cerebral tissue. His trail-blazing work continued, and as early as 1913 he used motion pictures for clinical demonstrations. His magnificent use of photography has always been a valuable part of his papers, as well as a constant cause for turmoil with his publishers.

He was an opportunist of the first magnitude, as is readily evident from his studies on the peripheral nerves, made from the rich material of the World War. Likewise, the epidemic of encephalitis led to his

exhaustive work on the basal ganglia. His attack on the problem of epilepsy had, as its by-product, his mapping out of the human cerebral cortex. His determination of the dermatomes in man is another extremely valuable incidental study, made as a result of his therapeutic division of posterior roots. Similar also was his extensive work on chordotomy, not to mention the series of papers on cerebral tumors which he and his associates presented during his last decade.

Foerster's teaching was rare. There were two categories, the formal, didactic lectures to the undergraduates, which lasted for the better part of two hours, and the informal discussions with his associates and visitors, which lasted indefinitely. His demonstrations were as dramatic as his lectures were lyrical. These were the only opportunities his assistants had to learn from him, for his ward rounds were rarely compelling. By the second method, reserved for his associates and his visitors, teaching was dispensed over coffee after ward rounds, at the dinner table after his lectures and over beer or wine in the restaurant during his earlier years and in his home during the last few years. He would then discourse on any and every topic, including art, literature, history, music and any branch of medicine, with ease and with authority. Indeed, one's general training from association with Foerster was just as valuable as the neurologic doctrine he was so happy in expounding.

To his visitors he was always most courteous. To those of his associates and graduate students with whom he had an even moderately warm bond he was extravagantly generous and hospitable, taking valuable time to show his favorite places in Silesia, and even distant parts of the continent, during a very busy period of his own life.

A profusion of papers flowed from the pen of Otfrid Foerster. This should be taken in its literal sense, for he wrote everything in longhand. It is said that he once had a secretary who was highly efficient and suited to his work. When she married and he found that her successor was not immediately as facile as she, he dismissed her and continued through the rest of his life, about a quarter of a century, without a secretary. Rumor has also had it that his publisher, Springer, had one worker who did nothing but read his writing in preparation for printing his papers and books.

His investigations dealt mainly with movement and sensation, in the course of which he contributed fundamental studies on man concerning every level, anatomic and functional, of the autonomic, motor and sensory mechanisms. One paper was a stepping-stone to the next, and he brought much of his work together exquisitely in the sections which he wrote for the "Handbuch der Neurologie," of which he was co-editor with Bumke and the editing of which took almost a decade from his productive scientific life. He was also editor for many years of the *Zeitschrift für die gesamte Neurologie und Psychiatrie* and associate

editor of the *Deutsche Zeitschrift für Nervenheilkunde* and the *Zentralblatt für Neurochirurgie.*

His life was a series of distinctions, honors and invitations. When Wilhelm Erb retired at Heidelberg in 1907, Otfrid Foerster was invited to become his successor, but Breslau was loath to let him leave. Since there was no professorship of neurology at that time, he was appointed a titular professor at the very early age of 35. Precedent was again set in 1911, when he organized the first department of neurology in Germany at the Allerheiligen Hospital. His abilities and renown led to the establishment of a professorship of neurology at Breslau, and he became professor ordinarius in 1922. He became president of the *Gesellschaft deutscher Nervenärzte* in 1924 and continued in this position through 1932.

In 1929 he was invited to become director of the neurologic section of the Kaiser Wilhelm-Institut, at Berlin-Buch, but he declined. He served as surgeon in chief pro tempore to the Peter Bent Brigham Hospital in October 1930. Soon thereafter the Rockefeller Foundation contributed very generously for the building and establishment of the Neurologisches Forschungsinstitut Breslau, of which he became director when it was opened in January 1934. He was Hughlings Jackson Lecturer at the Second International Neurological Congress at London in 1935. In 1937 the Society of British Neurological Surgeons honored him by making the long journey to Breslau to hold their annual spring meeting at his institute, which, since his death, has been called Otfrid Foerster Institut.

He became professor emeritus in 1938 but was recalled into university service in 1939, and since his wards at the Wenzel Hanke Krankenhaus were turned into a military hospital because of the war with Poland, he had to reestablish a department at the Allerheiligen Hospital. He worked there only a short time, for in June 1940 he was found to have very active pulmonary tuberculosis, of which he died on June 15, 1941, and his wife died of a similar infection two days later.

In closing his address as chairman of the fifteenth annual meeting of the *Gesellschaft deutscher Nervenärzte,* after having reviewed the lives of a number of important members who had died in the previous year, Otfrid Foerster made the following statement, which is most appropriately applied to himself:

> Obwohl die männliche Tugend nicht die Thräne verbeut, so müssen wir uns doch auf uns selbst besinnen. Und wenn wir nunmehr, den Trauerflor ablegend, zum Lichte zurückkehren, so wollen wir dessen eingedenk sein, dass wir unsere grossen Toten durch nichts höher ehren, als wenn wir ihrem Beispiele folgen, ihrem Vorbilde getreu weiter forschen, weiter arbeiten.
>
> Fortiter ac constanter. Nulla me terrent!

CARLOS GUILLERMO DE GUTIÉRREZ-MAHONEY

Abstracts from Current Literature

Physiology and Biochemistry

EXPERIMENTS ON CHEMICAL INTERFERENCE WITH THE EARLY MORPHOGENESIS OF THE CHICK: I. THE EFFECTS OF TETANUS TOXIN ON THE MORPHOGENESIS OF THE CENTRAL NERVOUS SYSTEM. PETER GRAY and HELEN WORTHING, J. Exper. Zool. **86**:423 (April) 1941.

It appears to be accepted that tetanus toxin produces its effects through the formation of some compound with nerve tissue. In order to discover how early in development this reaction can occur in presumptive brain cells, tetanus toxin was injected into the subgerminal cavity of chicks of from zero to twenty-four hours' incubation. Analysis of the results shows that the injections of tetanus toxin affected the central nervous system so as to produce two types of abnormality: a delay of the central nervous system in relation to the somite number and localized destruction of the anterior end. It is concluded that these effects may be due to an enzyme inhibitor which specifically affects the metabolism of the central nervous system.

WYMAN, Boston.

THE SENSORY BASIS OF OBSTACLE AVOIDANCE BY FLYING BATS. DONALD R. GRIFFIN and ROBERT GALAMBOS, J. Exper. Zool. **86**:481 (April) 1941.

The ability of bats to avoid obstacles while flying was measured by making them fly through a standardized barrier of metal wires. Tests were made with 144 normal bats and with several whose eyes, ears or mouths had been covered. "Blind" bats could not be distinguished from normal bats by their flight or obstacle avoidance. "Deaf" bats showed great reluctance to fly, and their ability to avoid obstacles was drastically impaired. "Gagged" bats, unable to emit supersonic notes, were handicapped just as much as deafened bats. No sense other than hearing was necessary for essentially normal obstacle avoidance. It is concluded that flying bats detect obstacles in their path by emitting supersonic notes, hearing these sound waves when reflected back to them by the obstacles and localizing the source of this reflected sound. This localization is probably accomplished by binaural activity of the auditory mechanism.

WYMAN, Boston.

EXPERIMENTAL CEREBRAL CONCUSSION. D. DENNY-BROWN and W. RITCHIE RUSSELL, J. Physiol. **99**:153 (Dec.) 1940.

Denny-Brown and Russell investigated the effects of experimental cerebral concussion in cats and monkeys. They found that a blow sufficient to cause "instant" acceleration of the head from zero to 23 feet (7 meters) per second was sufficient to produce death without causing macroscopic lesions of the brain. For the monkey the threshold was slightly higher.

They conclude that momentary deformity of the skull, labyrinthine stimulation or rise of intracranial pressure was not concerned in the phenomenon. Experimental concussions could also be produced in decerebrate cats, in which case the effect was on the medullary centers.

THOMAS, Philadelphia.

THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON CAPILLARY PERMEABILITY. D. ENGEL, J. Physiol. **99**:161 (Jan.) 1941.

Engel studied the effect of lumbosacral sympathectomy on the permeability of capillaries of the knee joint to dyes, chiefly fuchsin S, at the same time recording the temperature of the leg muscles as an indication of the changes in blood flow.

He found in a majority of both acute and long term experiments that, in spite of marked vasodilatation, the escape of dye through the capillaries was considerably reduced on the sympathectomized as compared with the normally innervated side. These results are in agreement with Asher's theory that the sympathetic innervation increases capillary permeability. However, the author points out that his results could have been due to changes in permeability associated with differences in oxygen supply to the capillary endothelium.

THOMAS, Philadelphia.

VASOCONSTRICTOR NERVES AND OXYGEN CONSUMPTION IN THE ISOLATED PERFUSED HINDLIMB MUSCLES OF THE DOG. J. R. PAPPENHEIMER, J. Physiol. **99**:182 (Jan.) 1941.

This investigation was concerned with changes in oxygen consumption in the muscles of the hindlimb associated with changes in blood flow produced by various means. When changes in blood flow were brought about by changes in perfusion pressure without nerve stimulation, the oxygen consumption was relatively unaffected. When the blood flow was reduced by stimulation of vasoconstrictor nerves, the oxygen consumption was greatly reduced. On the contrary, when the blood flow was reduced by the action of epinephrine, the oxygen consumption was generally increased. The author is inclined to reject the theory that nerve stimulation has a direct effect on tissue metabolism. He favors the view that the effects on oxygen consumption result from changes in the distribution of blood within the muscle. Numerous experiments seemed to support this hypothesis.

THOMAS, Philadelphia.

THE EFFECT OF ADRENALIN [EPINEPHRINE] ON NERVE ACTION POTENTIALS. E. BÜLBRING and D. WHITTERIDGE, J. Physiol. **99**:201 (Jan.) 1941.

Intra-arterial injections of epinephrine were found to increase the action potentials developed in affected nerve trunks in response to submaximal, but not to maximal, stimuli; the effect was therefore to lower the threshold of the nerve fibers to electrical stimulation. The effect of epinephrine was much greater in fatigued nerves. The spike in the action potential was frequently reduced by epinephrine, presumably because the fibers involved were highly susceptible to anoxia. It was noted incidentally that the tension of the innervated muscles was affected far more than the action potential in the nerve fibers. Increase in muscle tension often began before any change in the action potential could be detected and frequently outlasted the change in the nerve fibers. The authors suggest that the effect of epinephrine on the nerve-muscle junction should be investigated.

THOMAS, Philadelphia.

ROLE OF CEREBRAL EDEMA IN THE PATHOGENESIS OF CONVULSIONS. PAULO PUPO, Arq. Serv. assist. psicopat. estad. São Paulo **5**:16 (March-June) 1940.

Convulsions were induced in rabbits by means of 0.5 cc. of metrazol injected into a vein of the ear. Some of the animals were killed during the induced convulsions. Two died during such seizures. In some animals convulsions were repeatedly induced over a period of three months. In the brains of the rabbits killed during or immediately after the induced convulsions relatively large areas of cerebral edema were found, with no injury to the parenchyma of the cortex or distortion of its cytoarchitectonics.

The effect of intravenous injections of hypertonic solutions of dextrose and of distilled water on the convulsive threshold in rabbits was studied. In each of five experiments it was noted that the dose of metrazol necessary to induce a convulsion dropped from 0.2 or 0.3 cc. to 0.1 cc. after the injection of distilled water. Induction of edema of the brain lowered the convulsive threshold. After injection of a hypertonic (50 per cent) solution of dextrose the amount of metrazol necessary to induce a convulsion had to be increased to 1.6 cc. (five times the usual

dose). The period of latency before the convulsion appeared increased from six or seven to fifteen seconds. Dehydration therefore definitely raised the convulsive threshold.

A trephine opening was made in 2 dogs. In 1 dog a large frontotemporal opening was made and convulsions were induced by faradic stimulation of the brain. Engorgement of vessels and cerebral edema preceded the convulsion. The brain bulged through the trephine opening. Metrazol was used to produce convulsions in another dog which was anesthetized by chloroform and had a trephine opening. Immediately after the injection there was fleeting pallor of the brain, due to vascular constriction followed by congestion and cerebral edema.

SAVITSKY, New York.

FUNCTIONAL IMPORTANCE OF THE MOTOR AREA OF THE CORTEX FOR VISION IN DOGS. R. THAUER and F. STUKE, Arch. f. d. ges. Physiol. **243**:347, 1940.

Thauer and Stuke developed a method which permits one to determine exactly the visual field in dogs. The animals fixed on an object (for example, a lump of sugar) in the center of the perimeter, and a second object was moved from the periphery toward the center. When the border of the field was crossed the animal made slight movements of the eyes and/or of the head. In 10 normal dogs the lateral border of the field was found between 100 and 125 degrees and the medial border between 30 and 45 degrees. Eleven extirpations of the motor area and four extirpations of the occipital region were performed in 11 dogs. Extirpation of the motor area produced disturbances of the optomotor reactions which simulated visual defects. The visual capacity in the field contralateral to the extirpated motor area was, however, preserved. This could be demonstrated by combining the extirpation of the motor area on one side with the extirpation of the contralateral visual cortex in the occipital lobe. Such animals showed hemianopia corresponding to the lesion of the occipital lobe, but they were not blind. The authors suspect that the loss of optomotor reactions after extirpation of the motor cortex is due not only to loss of motor functions but also to disturbances of higher functions. Although the visual capacity was preserved in the field opposite the extirpated motor area, food placed in this part of the field failed to arouse the attention of some of the animals on which operation was performed. Furthermore, some dogs showed disturbances of orientation in space for a few days after the extirpation of the motor area, indicating a possible diminution of the cortical functions in toto following the operation.

SPIEGEL, Philadelphia.

ACETYLCHOLINE CONTENT OF SENSORY NERVES. K. LISSÁK and J. PÁSZTOR, Arch. f. d. ges. Physiol. **244**:120, 1940.

In former experiments stimulation of isolated nerves in vitro demonstrated that during stimulation acetylcholine is released from cholinergic and epinephrine from adrenergic nerves. Thus the nerves themselves contain and give off the substances that correspond to the mediator substances in the peripheral endings. In view of contradictory statements in the literature regarding the acetylcholine content of sensory nerves, the authors reexamined this question, using the optic nerve, the optic tract and the saphenous nerve of dogs and cats. Extracts of the nerves were dialyzed against a physostigmine-Ringer solution, and the acetylcholine content of the dialysates was determined by the frog heart method. While the acetylcholine equivalent of somatic motor nerves is from 1 to 5 micrograms per gram of nerve, the sensory nerves contain much less acetylcholine. The average values of ten experiments on dogs were: optic nerve, 0.05 microgram; optic tract, 0.19 microgram; saphenous nerve, 0.02 microgram per gram of nerve. The question is not yet settled whether acetylcholine and epinephrine are indispensable to nerve conduction.

SPIEGEL, Philadelphia.

POST-TRAUMATIC PRESSURE ON THE BRAIN. F. J. IRSIGLER, Arch. f. klin. Chir. **200**:202 (Oct. 18) 1940.

Irsigler characterizes the changes which post-traumatic pressure on the brain produces in the brain itself and on the fluid spaces as follows: 1. Post-traumatic pressure on the brain develops in the majority of cases on the basis of reactive cerebral swelling which results from collateral edema around the traumatic lesion and which may gradually extend over the entire hemisphere. 2. This cerebral swelling as a rule produces clinical signs of a generalized increase in cerebral pressure three or four days after the trauma. Pressure symptoms which appear within the first two days, or even within the first twenty-four hours, after the injury are nearly always caused by an intracranial hematoma. Although practically the same form changes and mass deviations are produced by the cerebral swelling and by the pressure resulting from intracranial hemorrhage, the difference in time between the appearance of the symptoms of these two types of pressure is one of the most important factors in the differentiation of the two traumatic sequels. 3. Injuries to the brain may be followed by incarceration in the tentorial notch with pressure on the brain stem and the quadrigeminal plate. The result is compression of the aqueduct of Sylvius with hydrocephalus of the ventricle. The incarceration explains also certain symptoms of the midbrain, such as anisocoria or disturbances of the conjugated movements of the eyes, which occur in persons with injuries to the brain. Unilateral pupillary dilatation and unresponsiveness to light are not always indicative of an intracranial hemorrhage; they are merely signs of pressure on the tentorium of the midbrain, and thus may accompany cerebral swelling as well as hemorrhage.

J. A. M. A.

Meninges and Blood Vessels

DELAYED TRAUMATIC INTRACEREBRAL HEMORRHAGE. C. P. SYMONDS, Brit. M. J. **1**:1048 (June 29) 1940.

That Dubois was able to find only 8 cases of delayed traumatic apoplexy among 1,700,000 cases of accidental injury collected by the Caisse Nationale Suisse is suggestive of the rarity of this condition. The hemorrhage may occur early or late. When it occurs within a few weeks of injury, it is probably the result of traumatic weakening of an arterial wall. Clinically, it may be difficult to differentiate early hemorrhage from ruptured congenital aneurysm. The author reports a suspected case of this type in a 42 year old man which followed a cerebral injury sustained ten weeks previously. The diagnosis was not definite because there was uncertainty as to the traumatic origin of the hemorrhage.

Late traumatic apoplexy, clinically similar to cerebral hemorrhage, may occur years after injury. This is explained by hemorrhage into a cyst caused by intracerebral hemorrhage at the time of injury. Symonds describes chronic intracerebral hematoma, or intracerebral hemorrhage resulting from cyst formation with progressive increase in volume, as another manifestation of delayed traumatic apoplexy.

ECHOLS, New Orleans.

ERYTHROMELALGIA. E. D. TELFORD and H. T. SIMMONS, Brit. M. J. **2**:782 (Dec. 7) 1940.

Telford and Simmons state that erythromelalgia, a condition first described in 1878 by Weir Mitchell, is a rare disease. They have seen only 4 cases in a period of nine years at a clinic for neurovascular disease. The condition usually affects young women and is characterized by redness and burning pain of the lower extremities, which increases in severity and is brought on by warmth and exercise. The cause of erythromelalgia is unknown. The diagnosis may be confused with the painful rubor frequently associated with poor peripheral circulation. Treatment formerly was symptomatic. The authors suggest treating the severe

intractable forms by section of the sympathetic nerve chain. They have treated 3 patients with lumbar ganglionectomy, with excellent results.

ECHOLS, New Orleans.

DOUBLE INFECTION OF THE MENINGES WITH MENINGOCOCCUS AND GAERTNER'S BACILLUS. K. J. GUTHRIE and T. ANDERSON, Brit. M. J. **1**:193 (Feb. 8) 1941.

Guthrie and Anderson report a fatal case of double infection of the meninges with Meningococcus and Gaertner's bacillus in a 14 month old infant. This case is of further interest because organisms of the Salmonella group only rarely invade the meninges. The authors call attention to the fact that Salmonella meningitis ordinarily affects infants rather than older children or adults. Four cases similar to the one recorded were found in the literature. The authors suggest as a possible explanation of such double infection "that a primary inflammation of the meninges by affecting the local capillaries and increasing the permeability of the endothelium may predispose to a secondary meningeal infection."

ECHOLS, New Orleans.

SYNDROME OF THE ANTERIOR CHOROIDAL ARTERY. J. O. TRELLES and J. LAZARTE, Rev. de neuro-psiquiat. **2**:546, 1939.

Trelles and Lazarte report a case of occlusion of the anterior choroidal artery. The patient, a white woman aged 50, single, had a family history of arteriosclerosis. Two months before she came for examination she commenced to have progressive weakness and loss of strength in the right arm, with swelling of the hand. In the course of a few weeks the right leg became similarly affected and she had difficulty in walking. At about the same time she became able to see only with great difficulty, owing to considerable reduction of the visual field. Two months after the onset of the illness she found that she was unable to write and sought medical attention. At this time she walked with great difficulty and had to be assisted. The right leg dragged somewhat, and the toe was pointed inward. The arm was held close to the body in semiflexion and pronation. There were contractions of the four last fingers of the right hand. Neurologic examination showed that the right half of the body had lost its normal mobility; this was more pronounced in the cervical and brachial regions and in the distal portions of the extremities. There were considerable loss of strength and limitation of passive movements, although hypertonia was not evident. The deep reflexes were increased on the affected side and somewhat brisk on the other. The right plantar reflex was of extensor type, and there was ankle clonus. The Chaddock, Gordon and Oppenheim signs were elicited. No trophic or sphincteric disturbance was noted. Touch, temperature and pain sensibilities were slightly disturbed, as was deep sensibility. Stereognosis was normal. Examination of the cranial nerves showed right homonymous hemianopia, with slight dilatation of the right pupil. The right side of the face showed hypesthesia, hypalgesia and widening of the palpebral fissure, with weakness of the right side of the lips. The tongue protruded to the right. Articulation was somewhat difficult, but true dysarthria was not present. The psychologic examination showed a certain amount of unproductivity, with some affective lability and loss of memory. Laboratory examinations revealed nothing remarkable.

The patient was examined two months later. The paralysis of the right side had progressed considerably and was still more pronounced in the upper extremity —being present to a degree at which the fingers could scarcely be moved at all. The reflexes continued to be increased, and the Babinski sign was positive. Sensation also had become more involved in all forms. There was vasoparalytic edema of the right arm, most marked in the dorsum of the hand. The abdominal reflexes were abolished, and the Babinski, Chaddock, Gordon and Oppenheim signs had become positive on both sides. Examination of the cranial nerves showed the right homonymous hemianopia previously noted with, in addition, abolition

of the corneal reflex on the right side, hypesthesia of the face on the same side and paralysis of the tongue. Difficulty in speech continued.

Because of the slow progressive course of the symptoms and their continuation in spite of treatment, this case was regarded as one of vascular origin due to softening. The picture is not characteristic of that caused by softening in the distribution of the anterior cerebral or of the sylvian artery. On the other hand, there is some similarity to the syndrome caused by a lesion of the posterior cerebral artery. In the latter condition, however, alexia, mental disturbances and symptoms of thalamic involvement are more marked. In the case presented there was no aphasia or alexia or evidence of mental disturbance. The authors believe that the area affected was probably that supplied by the anterior choroidal artery, the syndrome of which is characterized by contralateral hemiplegia predominating in the cervical and brachial regions, hemianesthesia and hemianopia, with which there may appear vasomotor and trophic disturbances.

NORCROSS, Toledo, Ohio.

THE CEREBRAL VESSELS IN CASES OF HYPERTENSION. H. E. ANDERS and W. J. EICKE, Arch. f. Psychiat. **112**:1 (Aug.) 1940.

Anders and Eicke report on the results of studies of the cerebral vessels in 36 cases of hypertension, as compared with those in 26 cases in which the blood pressure was normal. Serial sections of the vessels were made in both groups. The most important changes in the vessels consisted in hypertrophy of the media, arteriosclerosis and hyalinization. The hypertrophy of the media, which was found particularly in the large and middle-sized arteries, was especially frequent in young and middle-aged persons. Arteriosclerosis was marked and was found not only in the vessels at the base of the brain but also in the branches of the convexity. The most important change was hyalinization, a term which the author uses in the same sense as the "fibrinoid necrosis" of Staemmler and the "arteriosclerosis" of Aschoff. It is found in all the branches and smaller twigs, the cortex being as much affected as the basal ganglia. The specific characteristics of this change consist in its segmental occurrence, the swelling of the endothelial cells, the loss of elastic tissue and the absence of focal lipoid accumulations. It is important to note that the hyalinization was found in all the cases of hypertension whereas it was absent in all of the control cases.

The authors conclude that apoplectic, massive hemorrhages in hypertensive persons depend practically always on hyalinization, the hemorrhage being preceded by aneurysm. The extent of the hemorrhage depends on the caliber of the hyalinized vessel, and the reason for the frequent occurrence of hemorrhage of the striolenticular artery is to be found in the fact that it is the largest arterial branch of the brain. The clinical importance of hyalinization lies primarily in the fact that it so frequently causes hemorrhage. This need not always be in the form of a very large hemorrhage, since small and medium-sized hemorrhages may give rise to so-called preapoplectic manifestations. These may, then, under certain circumstances become the substratum of mental changes.

MALAMUD, Worcester, Mass.

Diseases of the Brain

PRECHIASMAL SYNDROME PRODUCED BY CHRONIC LOCAL ARACHNOIDITIS. WALTER I. LILLIE, Arch. Ophth. **24**:940 (Nov.) 1940.

Prechiasmal and chiasmal inflammatory lesions which produce a slowly progressive syndrome suggesting tumor can be subdivided into two main groups: basal gummatous meningitis and chronic local arachnoiditis. The former is diagnosed on the basis of serologic and cytologic changes in the cerebrospinal fluid. The latter usually presents a clinical syndrome so like that of tumor that it is

almost impossible to predicate the underlying lesion. Even the roentgenographic picture, which in instances of arachnoiditis is usually normal, does not eliminate a space-taking lesion. The fundus is not characteristic of either arachnoiditis or a space-taking lesion. The fields of vision are not characteristic. Ventriculography does not assist, but encephalography is of real service. The roentgenologist usually reports that the pathways of the subarachnoid fluid are somewhat interfered with at the vertex, the cisterna chiasmatica is irregular and deformed and compensatory channels are apparent in the frontal and occipital poles. Slight cortical atrophy is suggested by the enlargement of the pathways around the islands of Reil and the occasional presence of a very large channel between the convolutions over the vertex. These encephalographic findings are strongly against the existence of a space-taking lesion within the cranium.

The ophthalmologist therefore, with the ocular symptoms and signs of chiasmal lesion plus the encephalographic findings, should be able to predicate the underlying pathologic process. In fact, this chiasmal syndrome when associated with roentgenographic evidence of a normal sella and clinoid processes, should always be considered primarily as arachnoiditis until the encephalogram is made. While surgical treatment is essential here, as in the case of space-taking lesions, the neurosurgeon at least will know, within reasonable limits, the pathologic condition present and will be guided thereby.

SPAETH, Philadelphia.

ARHINENCEPHALY WITH ASSOCIATED AGENESIS OF THE CORPUS CALLOSUM AND OTHER ANOMALIES. HAROLD SHRYOCK and ROBERT S. KNIGHTON, Bull. Los Angeles Neurol. Soc. **5**:192 (Dec.) 1940.

Shryock and Knighton report 2 cases of congenital deformity of the brain. In the first, a female white child died of convulsions and pulmonary atelectasis seventeen hours after birth. There were harelip, cleft palate, imperforate nares and microcephaly, with closure of the fontanels. Autopsy revealed that the falx cerebri and the superior longitudinal sinus were absent and that the tentorium was attached to the line of the lambdoid suture. The brain weighed only 180 Gm., and the gyri were large and simple. The dorsal longitudinal fissure was incomplete, and the two hemispheres were united anteriorly. The olfactory bulbs, tracts and trigones were absent, as were the corpus callosum, the septum pellucidum and the body and columns of the fornix. The third ventricle was a shallow grove, and the two lateral ventricles were continuous across the midline. The hippocampal commissure and rudiment arched across the midline anterior to the pineal body and descended on each side into a rudimentary hippocampal gyrus. The medial and lateral geniculate bodies were barely indicated, and the optic tracts could not be found. The leptomeninges covering the cerebellum were thick and vascular; the circle of Willis was incomplete, and the cerebellum itself was grossly normal. Histologically the cerebral cortex was reasonably normal except for heterotopias in the hippocampal region. The pyramidal tracts were absent.

In the second case, a slightly premature female Negro child had an encephalomeningocele, in the left occipital region, which became gangrenous and caused death forty-eight days after birth. The head was small, the fontanels were open and the ventricles distended. The median longitudinal fissure passed from the mid-occipital region diagonally forward and toward the left, dividing the brain into a small left and a large right hemisphere. There was microgyria, involving especially the small left hemisphere. The olfactory bulbs, tracts and trigones, the optic tracts, the corpus callosum and the fornix were absent. The mamillary bodies were rudimentary, and the brain stem was twisted and misshapen. Heterotopic cortical tissue was observed in the lateral wall of the right ventricle, and ependymal rests were seen in the left thalamus. The third ventricle was not present, the right and the left thalamus being fused and the two lateral ventricles being in communication through an opening dorsal to the thalami.

The authors assert that incomplete separation of the hemispheres represents an early arrest of development. The development of the neopallium despite arrested

development of the archipallium indicates, they think, that ontogeny does not recapitulate phylogeny in the development of the human brain. They think the deformities described should not be considered atavisms, but should rather be regarded as due to arrest of development resulting from early metabolic disturbances.

MACKAY, Chicago.

INTRACRANIAL TUMORS OCCURRING IN THREE MEMBERS OF A FAMILY. GEORGE H. PATTERSON and FRANK M. ANDERSON, Bull. Los Angeles Neurol. Soc. **5**:218 (Dec.) 1940.

Patterson and Anderson report the occurrence of closely similar vascular tumors of the brain in a father and 2 sons. The father, aged 49, had a large cystic tumor of the left cerebellar hemisphere. Microscopically, there were numerous vascular spaces, closely and regularly placed, thin-walled vessels and connective tissue stroma, with newly formed blood vessels. The younger son, aged 23, had a large parasagittal angioblastic meningioma on the right side, containing many large vascular spaces, newly formed blood vessels and giant cells. The older son, aged 29, had a cyst of the right cerebellar hemisphere, but no tumor nodule was seen at operation. No retinal tumors were present in either son. Patterson and Anderson point out the histologic similarity between the angioblastic meningioma and the cerebellar hemiangioblastoma of Lindau's disease and emphasize the occurrence of the two types in a hereditary succession, an association not heretofore reported.

MACKAY, Chicago.

TWO CASES OF STATIONARY DEMENTIA PARALYTICA. C. I. URECHIA and M. MÜLLER, Confinia neurol. **3**:157, 1940.

Urechia and Müller report 2 cases of stationary dementia paralytica, in 1 of which the disease lasted twenty-two and in the other fifteen years. The first case was characterized by slight dementia with paranoid and grandiose ideas; the spinal fluid became normal with treatment. The second case was one of simple schizophrenia with hallucinations; the spinal fluid after treatment showed only a slight increase in protein. Pathologic examination showed moderate meningoencephalitis with degenerative changes and with but slight evidences of inflammation in 1 case and none in the other. The authors conclude that in stationary dementia paralytica a degenerative process is present with little or no inflammatory change but with some scarring, which may result from a preexisting infiltration.

DE JONG, Ann Arbor, Mich.

THUMB-MOUTH AGNOSIA: A SPECIAL FORM OF GERSTMANN SYNDROME. L. VON ANGYAL, Confinia neurol. **3**:245, 1940.

Von Angyal describes 3 cases of the Gerstmann syndrome in which finger agnosia was almost completely limited to the thumb and was accompanied by mouth agnosia. Other symptoms in these patients pointed to lesions posterior to the postrolandic convolution, in the angulo-occipitotemporal area. There was no acalculia, and von Angyal regards these cases as representing a special variety of the Gerstmann syndrome.

DE JONG, Ann Arbor, Mich.

NEUROLOGIC DISTURBANCES IN ACUTE HYDROCYANIC ACID POISONING. MAX WERNER, Deutsche Ztschr. f. Nervenh. **151**:123, 1940.

In the majority of cases hydrocyanic acid poisoning either produces no signs at all or brings about quick death. Cases of chronic poisoning have been reported. In these, as in cases of carbon monoxide poisoning, the symptoms are those of disturbances of the cerebellum, the basal ganglia and, sometimes, the diencephalon. Werner reports the case of a 32 year old galvanizer. He had, erroneously, added

sodium bisulfide, instead of sodium thiosulfate, to sodium cyanide. Foam formation occurred in the mixture, and the patient left the room immediately. He felt dizzy, collapsed and was unconscious for several minutes. He then complained of feelings of apprehension, anxiety, heartache and cold. In addition, he suffered from headache and dizziness. After three days he showed muscular hypotonia and adiadokokinesis, the Romberg sign was positive and he had attacks of profuse perspiration and cyanosis of the hands and feet. One week after his accident left inner ear deafness developed, whereas the left labyrinth was hyperirritable. This disorder of the eighth nerve is explained as "neuritis" and is compared to similar disturbances associated with carbon monoxide poisoning. A cisternal puncture which was performed three months after the accident yielded fluid under normal pressure, with normal protein and sugar contents and a normal colloidal gold reaction. The signs and symptoms cleared completely in three months, and the disturbance of the eighth nerve, headaches and cyanosis of the extremities improved. The headaches had been coincidental with the attacks of cyanosis of the extremities.

ADLER, Boston.

SEQUELAE OF INSOLATION IN THE CENTRAL NERVOUS SYSTEM. GUSTAV SCHMIDT, Deutsche Ztschr. f. Nervenh. **151**:146, 1940.

Clinical symptoms resulting from sunstroke may disappear, but when the condition is serious they may be present even after many years. Schmidt discusses a case in which, in his opinion, encephalograms demonstrated a relation between the acute stage of the disease and its sequelae. A 24 year old man paraded in military formation, under a scorching sun. After a few hours he suffered from nausea and vomiting. He spent the rest of the day lying in the sun. In the evening he became delirious and comatose. On examination there were stiffness of the neck and paresis and "cramps" of the right arm. A lumbar puncture, which was performed six days later, yielded clear fluid with a normal protein and cell content. The fluid was "under increased pressure," but absolute values were not recorded. Headaches and vomiting continued for one month, when several epileptic attacks occurred. These were followed by motor aphasia and right hemiplegia. The attacks continued in spite of the administration of bromides and phenobarbital. On reexamination five years after onset, the patient complained of weakness, headaches, difficulty in urination, dizziness, nausea and vomiting. The tendon reflexes were more active on the right than on the left, and strength and superficial sensation were diminished on the right side. The spinal fluid was normal, with a pressure of 120 mm. of water. Encephalographic examination, during which 100 cc. of air was injected, revealed marked enlargement of the ventricles and a shift of the ventricular system to the left. The left side of the ventricular system was more enlarged than the right. The author explains this change as resulting from the sunstroke and refers to another case in which autopsy, six days after insolation, showed thickening of the leptomeninges and multiple softening of the cerebral substance which were caused by intracranial hematomas of several extracerebral arteries.

ADLER, Boston.

LESIONS OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM FOLLOWING SULFAPYRIDINE THERAPY. H. PLUEGGE, Deutsche Ztschr. f. Nervenh. **151**:205, 1941.

Within the last few years injuries to the nervous system caused by sulfanilamide have been observed. Neuritis, polyneuritis, myelitis and encephalomyelitis have been reported to be caused by this drug or its derivatives. Pluegge refers to the report in the German literature of a case of sciatica and to the report in the American literature of 2 cases of encephalomyelitis following sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) medication. To these he adds 1 case each of polyneuritis

and neuromyelitis which occurred after treatment with this drug. The first patient, suffering from meningococcic meningitis, was given 21 Gm. of sulfapyridine in seven days, together with serum therapy. The spinal fluid became normal on the sixteenth day of the illness. On the tenth day there was a severe allergic reaction, and on the twenty-sixth day polyneuritis developed. This was restricted to the femoral, tibial and peroneal nerves. There were weakness and loss of reflexes in the legs, but little or no sensory disturbance. The neuritis failed to improve with various forms of treatment. The second patient, also suffering from meningococcic meningitis, was treated with sulfapyridine. Six weeks after the onset, at which time the cerebrospinal fluid had returned to normal, weakness, ataxia and loss of the tendon reflexes in the legs were noted. Two weeks later urinary difficulties developed. All the neurologic signs were improving when the patient was seen last, three months after the onset of the complications. ADLER, Boston.

HEREDITY OF PERIODIC PARALYSIS. R. GAUPP, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:108 (July) 1940.

Gaupp reports on three families with periodic paralysis. The first family came from Schleswig-Holstein. In six generations, 36 of the 136 relatives had periodic paralysis. There were 18 men and 18 women. The diagnosis was doubtful in only 4 cases. Transmission was apparently dominant, with no sex linkage.

The second family came from Alsace and Baden. In four generations, 14 of 39 members had periodic paralysis. There were 6 women and 4 men. The diagnosis was uncertain in only 2 cases.

In the third family a brother of a patient with an unquestionable case of the disease had two attacks of transitory paralysis. A maternal uncle died at the age of 35, a few hours after the onset of a paralysis of unknown nature.

SAVITSKY, New York.

ANATOMIC EVIDENCE OF PICK'S DISEASE IN TWO GENERATIONS. GEORG FRIEDRICH, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:311 (Sept.) 1940.

Friedrich reports the occurrence of Pick's disease in two generations. The mother became ill at the age of 47 and died at 50. The onset of her illness was insidious. She became unusually quiet and at times aimlessly restless. She was forgetful, showed defects of judgment, committed sexual indiscretions, stole and became rather childish. She was noted as irritable, though more often as indifferent and dull. During this first period, which lasted about a year, she showed evidence of intellectual enfeeblement. In a second stage, which lasted two years, she showed persistent lack of initiative, with occasional periods of agitation. During the last nine months of her illness she showed increasing mental deterioration, speech became incomprehensible and she lay helpless in bed. Her attention could be held to the last. There was marked atrophy of the frontal poles of the brain, with involvement especially of the anterior part of the first and second convolutions. The convexity of the frontal lobe was more involved than the orbital surface. The left side was more severely diseased than the right.

The son presented a more atypical picture. His illness began at the age of 35, and he died at 39. The onset was with weakness and signs referable to the pyramidal tract involving the left lower extremity. This weakness increased, and one year later the left upper extremity was involved. The right side also became weak and spastic. There were no mental symptoms until fifteen months after the onset of the motor weakness. It was then noted that he was irritable, but he showed no intellectual enfeeblement. Two and one-half years after the onset an aerogram showed internal hydrocephalus but no evidence of cerebral atrophy, even in the frontal region. About the time the air studies were made and spastic tetraplegia was marked, he began to show severe mental symptoms, which became progressively worse until his death from pulmonary tuberculosis one year later. He became confused and suspicious, showed difficulty in thinking, perseverated

often and had periods of marked agitation. Autopsy showed frontoparietal atrophy, more marked on the left side. There was atrophy of the gyrus supramarginalis and the superior parietal area. The precentral areas were severely involved. The pyramidal tracts in the brain stem and the upper part of the cord were not degenerated. The lower portion of the cord was not examined. The marked motor involvement was unusual. The author regards the son's condition as an atypical form of Pick's disease rather than as amyotrophic lateral sclerosis.

These 2 cases reemphasize the importance of heredity in the etiology of Pick's disease. No anatomic reports are available in the literature of a case in which this disease occurred in a parent and a child. SAVITSKY, New York.

Diseases of the Spinal Cord

BULBAR LESIONS OF TABES. R. L. NEGRI, Rev. neurol. de Buenos Aires **6**:108 (Jan.-March) 1941.

In this scholarly and well illustrated article, the author reviews the scanty literature on involvement of afferent bulbar tracts in cases of tabes. He then describes 2 cases in which bulbar lesions were found. In 1 case there had been symptoms suggesting ataxia of the jaws. In both cases there was degeneration of the tractus solitarius and of the descending root of the fifth nerve, but not of its nucleus or motor root. In 1 case there were also neuritic lesions of the rootlets of the vagus nerve, a change which might explain the pathogenesis of visceral and gastric crises in some cases. J. A. M. A.

DEGENERATIVE CHANGES IN THE SPINAL CORD DUE TO VASCULAR DISEASE. H. HEINLEIN and H. SELBACH, Deutsche Ztschr. f. Nervenh. **151**:71 (June) 1940.

Heinlein and Selbach report the case of a 58 year old man in whom paraplegia, at first spastic and later somewhat flaccid, developed rapidly and progressed steadily, with urinary and fecal retention, until his death from pneumonia, seven weeks after onset. He had, in addition, vertical and horizontal nystagmus and some weakness and muscular atrophy in the arms. The cerebrospinal fluid was normal except for a moderate first zone colloidal gold curve. The blood pressure was 110 systolic and 82 diastolic. Postmortem examination showed severe degeneration of the spinal cord in all its segments, with massive loss of white matter in all tracts. There was marked fibrosis of the walls of the arterioles, venules and capillaries throughout the cord, and the authors ascribe the degeneration of the nerve tissue to the vascular changes, the cause of which remains undetermined. The vessels elsewhere in the body seemed essentially normal, and the changes were unlike those seen in periarteritis nodosa. BRENNER, Boston.

OCCURRENCE OF THE DYSTROPHIC, NEURAL AND SPINAL FORMS OF PROGRESSIVE MUSCULAR ATROPHY IN ONE FAMILY. IMRE STERN, Schweiz. Arch. f. Neurol. u. Psychiat. **45**:447, 1940.

Stern summarizes the evidence tending to support the view that neural muscular atrophy, spinal muscular atrophy and progressive muscular dystrophy all have a common pathogenesis. Developmental anomalies of the central nervous system are fairly common in cases of progressive muscular dystrophy, and in the families of persons suffering from this condition various forms of nervous and mental disease are of frequent occurrence. Of greater significance are cases in which the clinical picture does not conform to any one of the three principal types of muscular wasting. In this connection, details are given of a case of muscular dystrophy in which sensory changes in the feet and marked atrophy of the muscles below the knee on one side were suggestive of the neural form of muscular atrophy. More than one type of muscular atrophy has been encountered in certain families. The

offspring of patients suffering with spinal muscular atrophy, for instance, may have progressive muscular dystrophy. Dystrophic muscular changes have been observed in cases of acute and chronic poliomyelitis, lethargic encephalitis, tabes dorsalis and cerebellar tumor. Similar changes have been produced experimentally by removal of parts of the sympathetic or parasympathetic nervous system. Clinical evidence is cited in support of the belief that diencephalic centers of the autonomic nervous system may be involved in cases of progressive muscular dystrophy.

Stern reports the cases of 3 siblings, each of whom had a different variety of muscular atrophy. The mother, father and 3 other children in this family were physically sound. The first patient, a woman aged 25, had a neural type of muscular atrophy; the onset of weakness at the age of 8 years was preceded by an attack of influenza and was accompanied by pain and paresthesias in the feet. Fibrillary twitching was noted in the small muscles of the hands, but wasting was more pronounced in the muscles of the feet and legs. Although muscular atrophy was likewise more marked peripherally in the second case, that of a youth aged 19, involvement was more diffuse, and fibrillary twitchings were observed in the lower as well as in the upper extremities. The onset had occurred with weakness in the hands four years previously, and symptoms of bulbar palsy had subsequently developed. Atrophy and fibrillary twitchings were noted in the tongue; the tendon reflexes were sluggish, but pathologic reflexes were not elicited. The patient was believed to be suffering from spinal muscular atrophy. The third patient, a girl aged 8 years, had progressive muscular dystrophy of the facioscapulohumeral type of Landouzy and Dejerine. Weakness of the muscles of the shoulders had become apparent one year previously, and there was some involvement of the muscles of the back and hips, as well as of the left quadriceps femoris muscle. The tendon reflexes were normally active, and fibrillary twitching was not observed.

The 3 foregoing cases are believed to furnish additional proof not only of the intimate relation of the various myopathies to one another but of the neurogenic origin of progressive muscular dystrophy. The studies of Ken Kuré suggest that the primary lesion in all these cases is to be found in the sympathetic or the parasympathic centers of the spinal cord. The type of muscular atrophy, according to this view, would be determined by the location and extent of the heredodegenerative process within the spinal cord.

DANIELS, Denver.

HEMORRHAGIC MYELITIS OR MYELOMALACIA. M. ELLERMAN, Acta psychiat. et neurol. **15**:291, 1940.

Ellerman reports the history of a syphilitic patient aged 44 with a six day prodrome of febrile disease of the upper respiratory tract followed by paresthesias in the legs for seven days, then paraplegia and, two days later, complete paralysis with loss of sensation from the abdomen down and rectal and urinary incontinence. The cerebrospinal fluid as obtained by lumbar puncture was normal except for a slightly increased initial pressure (170 mm.) and a total protein content of 144 mg. per hundred cubic centimeters (Bisgaard). The sensory level gradually rose, and the patient died of respiratory failure. Microscopic examination showed profound hemorrhagic necrosis of nearly the entire spinal cord, with polymorphonuclear leukocytic infiltration.

BRENNER, Boston.

EFFECT OF COMPRESSION OF SHORT DURATION OF THE ABDOMINAL AORTA IN THE RABBIT. B. REXED, Acta psychiat. et neurol. **15**:365, 1940.

Complete occlusion of the abdominal aorta of the rabbit for less than fifteen minutes produces no permanent functional residua in the neuromuscular system of the hindquarters. Similar occlusion for more than about twenty-five minutes results in permanent flaccid paralysis with rapid muscular atrophy, due to necrosis of the spinal cord. With intermediate duration of the occlusion there appeared in some animals permanent spastic paralysis of the hindquarters with complete

sensory loss, loss of sphincter control and partial reaction of degeneration in the affected muscles. Rexed attempts to correlate this observation with Häggqvist's statement that in experimentally induced anemia the small cells of the anterior horns and the ventral root fibers issuing from them survive longer than do the larger anterior horn cells and the coarser root fibers. The author does not report on postmortem examinations of the spinal cord or peripheral nerves in his own experimental material.

BRENNER, Boston.

Special Senses

SPARING AND NONSPARING OF "MACULAR" VISION ASSOCIATED WITH OCCIPITAL LOBECTOMY IN MAN. WARD C. HALSTEAD, A. EARL WALKER and PAUL C. BUCY, Arch. Ophth. **24**:948 (Nov.) 1940.

The authors report 2 cases which permitted unusual opportunities for studying in detail the cortical projection of the macula. The first case was one of complete occipital lobectomy for a tumor, a mixed astrocytoma and polar spongioblastoma; in the second case a similar operation was performed because of a glial cyst, the microscopic features being one of a typical oligodendroglioma. In 1 case there occurred macular sparing and in the other macular splitting. The authors' comment on these 2 cases is so pertinent that it is quoted here.

"In the 2 cases of occipital lobectomy considered in this report it was found that the patients remained intelligent, cooperative and capable of accurate fixation, thus making possible careful examination of the central visual fields. Right hemianopia with noncongruous maximal sparing of 2.5 degrees for brightness and color was found under test conditions, providing direct control of accuracy of fixation in the instance of the patient with the left occipital lobectomy. Sparing of 1.25 degrees for form was also found in this patient. Left homonymous hemianopia with splitting of the macula was found in the instance of the patient with a right occipital lobectomy. This has been found repeatedly on examinations made during the six months after the operation. In the first case complete removal of all striate cortex has been verified histologically. In the second little, if any, striate cortex remained after lobectomy. Only the most anterior extremity of occipital lobe area could have been left.

"The paradox presented by the foregoing cases does not seem open to solution in terms of any of the present hypotheses concerning the arrangement of the visual system. The theory of a callosal geniculocalcarine bundle, propounded by Pfeifer and elaborated by Foerster and by Penfield, Evans and MacMillan, has found no corroboration in comparative neurophysiologic (Maison, Settlage and Grether) or neuroanatomic investigations (German and Brody, Putnam and Poliak) and no support from the recent clinical study of Hyndman. The theory of aberrant macular fibers in the optic chiasm has been questioned by numerous investigators particularly on the basis of comparative material and has received no attention from recent workers. The possibility of retinal internuncial overlap in the macular region is not precluded by investigative studies, but no definite evidence has been produced in its favor. We realize that these theories do not explain the paradox presented. Yet we believe that the evidence afforded by the 2 cases is sufficiently well controlled both in terms of histologic control of the lesion and in analysis of the visual functions to show that the paradox is real and not apparent. The problem of the cortical projection of the macula is not yet adequately solved."

From the observations presented by the authors, it seems (1) that there is no necessity to postulate bilateral macular representation; (2) that a macula-sparing hemianopia indicates a lesion of the occipital lobe, and (3) that a macula-splitting hemianopia points to a lesion of the temporal lobe, or of an area anterior to this, with or without the occipital lobe being simultaneously involved. Lillie's statement, which correlates central scotomas resulting from lesions of the occipital lobe with peripheral and central field conditions referable to involvement of the same lobe, follows also, because of its significance.

"It is known from the clinical standpoint that vascular lesions rather than neoplastic lesions or calcified hematomas support the work of Holmes and Lister, who showed that a homonymous central scotoma is obtained if the macular area in the pole of the occipital lobe is involved. This is possible only when the occipital visual area or the optic chiasm is involved. There has never been a case reported in which a homonymous scotoma has been found as a result of a lesion in the temporal lobe or in the optic tract. The central scotomas resulting from lesions involving the optic chiasm are asymmetric; usually one scotoma is much more advanced than the other, and the central visual acuity is markedly reduced. The homonymous central scotomas resulting from a lesion of the occipital lobe do not affect the central visual acuity and are symmetric."

SPAETH, Philadelphia.

VISUAL FIELD DEFECTS ASSOCIATED WITH CEREBELLAR TUMORS. LAURENCE M. WEINBERGER and JOHN E. WEBSTER, Arch. Ophth. **25**:128 (Jan.) 1941.

While cerebellar tumors associated with severe visual loss due to papilledema are commonly observed, the field changes in the vast majority of cases of such tumors are only those of concentric contraction. Therefore the finding of a homonymous hemianopic defect must be explained on some other basis. Cushing and Walker expressed the belief that it resulted from the distended third ventricle pushing the optic nerves laterally against the carotid arteries so that the outer parts of the nerves were indented.

Weinberger and Webster analyzed 4 cases of homonymous hemianopic defects which appeared in a series of 150 cases of verified tumor of the cerebellum; in all 4 of these instances a ventriculogram showed a markedly dilated ventricular system. Necropsy in 2 of the cases verified this observation.

Bitemporal visual field defects appeared in a fifth case, and the presence of cerebellar tumor was also confirmed by air studies. In 3 other cases irregular defects not characteristic of any one condition were present, but the irregularity of the fields seemed to preclude a space-taking lesion of the cerebellum. In 1 of these cases primary atrophy of the optic nerve was present; in all 3 instances ventricular dilatation was disclosed by the ventriculogram, and in 1 the necropsy showed generalized hydrocephalus.

The authors assert that although cerebellar tumors are thought not to produce field defects, it has been recognized by many writers that such defects may occur with internal hydrocephalus. Yet every cerebellar tumor eventually results in hydrocephalus. Clinical evidence also points to distention of the third ventricle resulting from cerebellar tumor as the primary cause of the field defects reported. Direct compression of the optic chiasm by a dilated fluid ventricle may give rise to bitemporal hemianopia, homonymous hemianopia and various unclassified defects. These probably depend on notching of the optic nerves and optic chiasm by the adjacent arteries plus the fact that the chiasm is not always in direct vertical relation with the third ventricle. Thus many and varied combinations of visual field defects may follow dilatation of the third ventricle.

SPAETH, Philadelphia.

OCULAR CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA. LUDO VAN BOGAERT, J. belge de neurol. et de psychiat. **40**:252 (May) 1940.

Visual difficulties accompanying pernicious anemia have been attributed to retinal hemorrhage, retinal or papillary edema and thromboses of the retinal arteries or veins, and optic neuritis and optic atrophy have been considered rare complications. Van Bogaert reports 2 cases in which atrophy of the optic nerve was an important finding, and he expresses the belief that visual symptoms may precede other symptoms of anemia. The atrophy of the optic nerve may be the result of demyelination, similar to the process present elsewhere in the neuraxis and, accordingly, not reversible. On the other hand, there may be less complete lesions, similar to those

associated with toxic processes involving the peripheral nerves, and in these instances there may be response to antianemic therapy.

DE JONG, Ann Arbor, Mich.

Diagnostic Methods

HEAD RETRACTION REFLEX. R. WARTENBERG, Am. J. M. Sc. **201**:553 (April) 1941.

Wartenberg calls attention to the head retraction reflex, which indicates that if a bilateral lesion of the pyramidal tract is present it must lie above the upper cervical portion of the cord, that is, in or above the brain stem. In the area of the face the jaw jerk, which is a purely trigeminal reflex, is usually tested first. Exaggeration of this reflex indicates a lesion of the corticopontile tracts above the motor nucleus of the fifth nerve. A greatly increased snout reflex indicates involvement of the corticobulbar pathways to some degree. The head retraction reflex may be elicited in different ways; all methods cause a sudden bending of the head. The best method appears to be tapping the upper lip, the observer sitting at the right side of the patient while the light is on the left. The head retraction reflex has never been found strongly positive in normal persons, even though other tendon reflexes are exaggerated. The reflex is most pronounced in cases of amyotrophic lateral sclerosis and has also been elicited in cases of lateral sclerosis, cerebrospinal syphilis and arteriosclerotic and other diffuse lesions of the brain, including essential hypertension. The most practical aspect of the reflex lies in the fact that in some cases it has been the only, and in others the outstanding, sign of a supracervical or a suprapontile lesion. It may facilitate the differential diagnosis of lesions of the high cervical portion of the cord and systemic degenerations of the spinal cord. It is suggested that a release of cortical inhibition must take place in the muscles that retract the head before this reflex can appear. Therefore the lesion must lie bilaterally in the corticospinal tracts above the anterior motor nuclei of the upper cervical segments. The head retraction reflex could thus be an expression of the mildest subclinical form of decerebrate rigidity.

MICHAELS, Boston.

A NEW VERTEBRA PROMINENS REFLEX. L. BENEDEK, Confinia neurol. **3**:220, 1940.

Benedek describes a reflex elicited in a patient with a tumor invading both cerebellar hemispheres. In this case pressure on the vertebra prominens elicited backward bending of the head and trunk as a constant tonic reflex. He states that the posterior lobe of the cerebellum controls forward bending of the body and the anterior lobe backward bending. Destruction of the posterior lobe results in loss of forward bending, and the stimulus of pressure on the vertebra prominens elicits the dominant action of the anterior lobe.

DE JONG, Ann Arbor, Mich.

ELECTROENCEPHALOGRAPHIC STUDIES ON PATIENTS WITH SYMPTOMATIC EPILEPSY. R. JANZEN and A. E. KORNMÜLLER, Deutsche Ztschr. f. Nervenh. **150**:283 (May) 1940.

Janzen and Kornmüller report a group of cases of cortical epilepsy, in a few of which electroencephalograms were taken during attacks; in the other cases records were made during free intervals. The authors found that the records taken during attacks showed the same electrical characteristics of primary foci as they had previously found to hold in their animal experiments. Using the same criteria for primary foci, the authors report that by analysis of the interseizure records they were able correctly to localize the lesion in each of 14 cases in which a subsequent operative or pathologic diagnosis was made.

BRENNER, Boston.

"Late Block" Following Injection of Iodized Poppyseed Oil. L. Benedek and A. Juba, Deutsche Ztschr. f. Nervenh. **151**:55 (June) 1940.

Benedek and Juba report a case of arachnoiditis at the level of the third and fourth dorsal segments in which combined puncture and other methods yielded no evidence of block. On cisternal injection of iodized poppyseed oil the bulk of the oil collected normally in the theca in two hours, though scattered drops were visible at the fourth dorsal segment. After three days, however, a relatively large mass of oil with a crescentic lower border was visible at the level of the third and fourth dorsal segments, and this remained unchanged for three days thereafter. Operation revealed arachnoiditis at this level. The subsequent clinical course of the patient is not mentioned. The authors report a case of syphilis of the central nervous system in which iodized poppyseed oil had been injected. Postmortem examination showed numerous small granulomas, which they interpreted as a meningeal reaction to droplets of the oil. They therefore recommend removal of the iodized oil at operation or by spinal puncture. Brenner, Boston.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

LEON H. CORNWALL, M.D., *President, in the Chair*

Regular Meeting, April 1, 1941

Metrazol as an Adjunct in the Treatment of Mental Disorders. DR. CLARENCE O. CHENEY, DR. DONALD M. HAMILTON (by invitation) and DR. W. LYNWOOD HEAVER (by invitation), White Plains, N. Y.

Since November 1939, 112 patients have been treated with metrazol at the New York Hospital, Westchester Division, White Plains, N. Y., and three months or more has elapsed since 104 of that number have completed treatment. The method of management of the patient during treatment is described, and the technic is demonstrated by colored moving pictures.

Of the 112 patients treated, 32 were men and 80 women. The ages varied from 17 to 66 years. The duration of symptoms before metrazol treatment varied from less than six months, in the cases of 25 patients, to a maximum of ten years; 29 patients had been ill from six to twelve months, 24 from one to two years and 34 for more than two years. According to the diagnostic grouping, there were 32 cases of dementia praecox, 51 of manic-depressive reactions, 19 of involutional melancholia, 9 of the psychoneuroses and 1 of psychopathic personality.

The results reported for the 104 patients who had completed treatment from three months to one year previously were as follows: Of 51 manic-depressive patients treated, 29 were at home, of whom 26 had recovered and 3 were much improved; 19 were in the hospital in an improved condition. Thus, 48 of the 51 patients were considered to have benefited from treatment, only 3 showing no improvement.

Of 16 patients with involutional psychoses who completed treatment, 13 were at home, of whom 10 had recovered and 3 were much improved; 2 were in the hospital in an improved condition. Thus, 15 of 16 patients were believed to have been benefited from treatment. Only 1 patient showed no improvement. The rapid gain shown by some of these patients, leading to prompt recovery when the outlook had previously seemed very poor, has been striking.

Of 8 psychoneurotic patients, 7 were at home, of whom 4 recovered and 3 were much improved. One remained in the hospital in an improved condition. All appeared to have benefited from treatment.

Of 28 patients with dementia praecox, 7 were at home, of whom 3 recovered and 4 were much improved; 11 others were in the hospital in an improved condition. Thus, 18 of 28 patients benefited from treatment, and 10 remained unimproved.

The 1 patient with a psychopathic personality had left the hospital unimproved two months after metrazol treatment. A recent communication had indicated that his condition was improved.

In summary, of the 104 patients who had completed treatment with metrazol not less than three months before, 57 were living at home, 43 of them recovered and 14 much improved, and 32 were in the hospital in an improved condition, several ready to leave shortly; 89 patients, therefore, were considered to have benefited from treatment. Fifteen patients were considered unimproved by treatment. There have been no deaths as a result of or in connection with the metrazol treatment.

We believe that none of the group of patients studied has been made worse by the use of metrazol, nor has evidence of permanent cerebral damage been seen.

Not infrequently, after a series of metrazol convulsions patients have shown varying degrees of confusion and some forgetfulness, lasting a few days or sometimes longer, but in all instances these symptoms have eventually disappeared. The patient who showed this organic reaction for the longest period returned to her former position as chief librarian in a large metropolitan library over six months ago; she is considered as efficient as before her illness, and better balanced. It is not maintained that metrazol treatment cures patients who would not eventually recover by other methods. From our experience, we believe that in patients who have the capacity to recover metrazol treatment brings about a change which facilitates other forms of therapy and accelerates recovery, so that residence in the hospital is shortened, sometimes in a strikingly dramatic manner. Its judicious use for this purpose is advocated.

DISCUSSION

DR. NOLAN D. C. LEWIS (by invitation): From various reports one must conclude that the results vary to a considerable extent from one clinic to another. It is possible that some of these differences are due both to the selection of the patients to be treated (some clinics taking only the young patients with an early stage of the disease, while others include every type) and to the refinements of the technic; for example, in two centers of investigation the technics in general or grossly may be the same but in the finer, but important, details may be very different.

Many workers neglect or purposely disregard the psychologic factors, while Dr. Cheney emphasizes the value of preparing the patient psychologically to prevent fear, and thus this reaction has not been outstanding in his series. Other workers, apparently not following this procedure, have even built up theories that the beneficial results are due neither to the convulsions nor to any metabolic changes but to the fear engendered by the aura, which is practically always acutely disagreeable (Good, R.: *J. Ment. Sc.* **86**:491 [May] 1940).

Dr. Cheney recommends psychotherapeutic attention because it reduces psychologic tension, and he also stresses psychologic aid following the period of treatment. He takes active measures to prevent the nausea and vomiting and the characteristic fractures of the vertebrae.

He expresses the opinion that metrazol in the favorable cases changes symptoms without affecting the underlying pathologic process but brings the patient to a higher level of adjustment, where he can gain insight and deal more rationally with his environment.

Changes in the brain, such as ischemic alterations in the cortex, hypertrophy and hyperplasia of the astrocytes (astroglia), and of the microglia to a lesser degree, and mild disturbances in the neuron cells, have been reported from Oslo, Norway, Northwestern University and the University of Georgia.

Dr. Cheney, like some other workers, has seen no clinical evidence of permanent damage to the brain.

It has been the hope of many investigators that metabolic changes responsible for the improvements could be discovered and then brought about by some means less radical, terrifying or energetic, but to date this has not been accomplished.

Although my associates and I are not quite ready to prove it statistically, we believe we are slowly establishing the fact that electric shock convulsive therapy is as efficient as the metrazol method; if this is so, then it is preferable, as the unpleasant effects of the metrazol procedure are automatically eliminated.

I agree with Dr. Cheney's conservative conclusions.

DR. T. R. ROBIE, East Orange, N. J.: May I ask Dr. Cheney if he has used curare in any of his cases?

DR. THOMAS K. DAVIS: When Dr. Cheney gets permission from the relatives of patients to carry out this procedure, to what detail does he go in describing the possible dangers, particularly the possible fracture of the spine?

DR. CLARENCE O. CHENEY: Curare has not been used, because of the unfavorable reports of the combined treatment of metrazol and curare in some series. We concluded there was no advantage in using it and have avoided the bad results reported by some of those who have employed it.

Regarding Dr. Davis' question about permission to use this procedure, we do explain the situation to the patient and relatives. The signed permission obtained before treatment is begun in each case includes a statement that the possible dangers have been described to the signer.

I agree heartily with what Dr. Lewis has said. Because I did not have time to read the whole paper, I did not indicate that the changes in the vegetative functions have, we consider, a great deal to do with the improvement of the patient. I agree with what Dr. Lewis said regarding the change in attitude of the patient toward the physicians, the nurses and the hospital. The patient feels that something has been done for him, and he is not so afraid of another breakdown. We have given repeated courses of metrazol treatment to a number of patients when the first one was not successful. No patient has had more than fifteen doses, and usually the number has been six or eight. We feel certain that harm may be done by continuously giving metrazol in an uninterrupted series, such as fifteen or twenty injections. If the patient does not improve after six or eight doses we stop the treatment for several weeks and then start another course; that possibly is the reason that we have not had permanent organic effects, which we believe may develop with long-continued, uninterrupted use of metrazol.

Analysis of Eighty-Eight Cases of Tumor of the Brain Occurring During Childhood and Adolescence. DR. JOSEPH H. GLOBUS, DR. JOSEPH M. ZUCKER (by invitation) and DR. JOSEPH E. RUBINSTEIN.

The clinical manifestations and anatomic features have been surveyed in 88 verified instances of tumor of the brain occurring in children, studied at the Mount Sinai Hospital and collected over a long period. In this study problems were investigated as to the type of cerebral tumor likely to be encountered in children, the clinical manifestations which may lead to an early and correct diagnosis and the results obtained from surgical intervention or roentgen therapy. Among some of the observations, it was noted that in younger children tumors in the posterior fossa are the more frequent, that those of the blastomatous variety are more common in the younger groups and that during certain periods, such as between the ages of 6 and 10 years, the incidence of tumor is lowest. It was also noted that the hemangiomatous variety of tumor is found most frequently in the cerebellum and that this has a long survival period. This type of tumor is rarely found among the young patients who die without operative intervention. It is striking that no pituitary adenoma was encountered in the series of tumors studied. A new form of tumor, described under the name infundibuloma, will be reported elsewhere by one of us (J. H. G.). It is also pointed out that a tumor often diagnosed as astrocytoma is essentially a vascular tumor in which glia elements of a reactive character are encountered in large numbers. The paper will be published in full elsewhere.

DISCUSSION

DR. BERNARD SACHS: I appreciate the work which Dr. Globus has done, and I am willing to accept his authority and his explanation of these tumors. I do not think I have any right to discuss this subject, except to make a few comments, based largely on personal studies of this subject and on personal experience. Personally, I have the distinct impression that these tumors of the brain are seen relatively more frequently in childhood and adolescence than later in life. No doubt embryonic rests are largely responsible for such tumors—aided and abetted by the frequent traumas suffered by younger patients.

I wonder whether the cystic formation which is so common in the tumors of childhood has not something to do with the impression of many that, taken as a

group, the cranial tumors in children bear a more favorable prognosis than do such tumors in adults. In connection with that I should like to cite an experience to which I have never referred in any meeting or publication. Forty-one years ago I saw a young woman, at that time a Bryn Mawr student, who began to manifest a combination of symptoms, such as vomiting, double optic neuritis, dizziness, intense headache and gradual involvement of the left arm and leg, that pointed at that time, when there was much interest in cortical localization, to a lesion in the motor area on the opposite side of the brain. On the strength of that, I advised an exploratory operation, and forty-one years ago that was no bagatelle! This was done by Dr. Arpad Gerster, with all the necessary precautions that the surgeon desired. On opening the skull a tremendous bulging and a very vascular surface were encountered. I can hear Dr. Gerster saying, "My God, I won't touch it; she will die on the table." That may have been interesting enough, but the sequel is more interesting. Nothing else was done, except that a trephine opening was made, and the operation was practically ended then and there. The result is curious. I saw that patient only a week ago. She is now about 61 years of age. She told me, when I tried to refresh my memory about the case, that Dr. Gerster told her mother he hoped the operation would be successful, but if not that she would be paralyzed for the rest of her life. As a matter of fact, the left side recovered completely, and the woman went through her life, up to the sixtieth year, without any symptoms other than the blindness, which, unfortunately, could not be cured. The patient walks three to six miles every day and has been a most useful citizen in every way; she is an intelligent person, and she has been one of the best social workers among the blind in this city and has helped them simply from her own experience. I thought it was worth while to relate this experience, simply as encouragement with the idea that, no matter what the histologic character of the tumor may be, the prognosis need not be too pessimistic. I am a great optimist, and I love these things which prove that some who were pessimistic have been wrong. My only explanation of the case has been that the release of the tremendous intracranial pressure was responsible for the decrease in size of the cyst. Here, at all events, was a case in which the operation was anything but what would be approved of nowadays but the result has been a remarkable one, and I do not think that many will be able to cite cases in which the patient has lived forty-one years after an attempt at cranial intervention. I should like to ask Dr. Globus about the frequency of these cystic formations in tumors in children and adolescents.

DR. IRA COHEN: I have a peculiar interest in this study, for a great many of the patients in the series were operated on in my service and the others were operated on at a time when Dr. Elsberg was doing the work at Mount Sinai Hospital. Therefore they span the period from the time when the surgeon was delighted to find a cyst and simply empty it, feeling that he and the patient were both fortunate, to the present, when it is recognized that not the cyst, but the tumor within the cyst, is the important factor.

Dr. Globus' statistics correspond closely with the results of similar studies made by others, such as those of Cushing (The Intracranial Tumors of Preadolescence, *Am. J. Dis. Child.* **33**:551-584 [April] 1927) and of Stern (Cerebral Tumors in Children, *Arch. Dis. Childhood* **12**:291, 1937). They illustrate the preponderance of infratentorial over supratentorial tumors of about 2 to 1. They also show that such tumors as meningioma, acoustic neurinoma and spongioblastoma, which make up about 50 per cent of cerebral tumors in adults, are rare in children. I was interested in the number of cases in Dr. Globus' series, 9 to be exact, of tumors in children under 1 year of age. In fact, some of these were prenatal. Dr. Sidney Gross (Tumors of the Brain in Infancy, *Am. J. Dis. Child.* **48**:739 [Oct.] 1934), reporting on tumors in children under 2 years of age, pointed out how infrequent they are.

I was also interested in the decrease in the number of tumors between the ages of 6 and 10 years which Dr. Globus showed. According to Cushing's graph and

the graph of Ley and Walker (Statistical Review of Two Hundred and Thirty Consecutive Cases of Intracranial Tumor, *Acta neuropath. Esthonia* **60**:52, 1936) this drop occurred at about the age of 16 years. Their explanation was that at this period the tumors peculiar to children were disappearing and the tumors found in adults were not being encountered with any great degree of frequency. Dr. Globus stated that Bailey also noted a drop between the ages of 6 and 10 years. It makes one wonder whether the tumors found in the first two years of life are not after all true congenital tumors, which make themselves known in the early years, and the tumors which begin to develop, say, after the tenth year are those which spring from tumor rests and that perhaps the general growth of the body and the changes in the body which begin to take place at that time may be factors in promoting growth.

The large number of hemangiomas which Dr. Globus reports is based on his usual careful study of the microscopic sections.

From the surgical standpoint I can state that at the operating table my colleagues and I do not depend on our impressions, but have a frozen section of the specimen made immediately; the impression of the operating surgeon and the final report from the laboratory coincide in the majority of cases, but I should hesitate, in encountering a tumor in a cyst, to make the gross differentiation of an astrocytoma and a hemangioma. They resemble each other closely.

From the clinical side, and here is an instance in which facts give place to impression, I always thought that convulsions would occur in cases of tumor of the brain in children no matter where the tumor was; yet, according to the figures, they are practically unknown in cases of infratentorial lesion.

The fact that a fair number of children with tumor of the posterior fossa do not have papilledema is not unknown. In a review I made some years ago I pointed out that 50 per cent of our patients, not only children but adults, come into the hospital without papilledema. We recognize the earliest signs of a cerebellar tumor in a child as listlessness and disinclination to play, coupled with occasional attacks of vomiting. This is often the outstanding early history.

Gentlemen, we have tonight had the pleasure of being present at the birth of a new tumor. With further study, or even without further study, we have seen infundibuloma put on the map and have added it to the list of fearful names we have to deal with. I think Dr. Globus has made a very good point in proof of the existence of such a tumor.

DR. A. A. BRILL: I am not going to discuss Dr. Globus' paper and get into any controversy with him on the subject of tumors, but it gives me great pleasure to add something to Dr. Sachs's interesting case, with which I know he is not going to disagree—perhaps for the first time. I saw the patient he described about thirty years ago. Dr. Sachs does not know that. She was brought to me because at that time she still refused to acknowledge that she was blind and consequently got into all kinds of accidents. She absolutely tore herself away from the reality of her sad situation and went out alone. She would not admit that she was blind; I had to treat her for some time to make her realize that she was really blind.

DR. BERNARD SACHS: I arise only to say that during that period I saw the young girl and she never denied to me that she was blind, nor did I have to make her believe she was blind. Otherwise, I agree with Dr. Brill.

DR. IRVING H. PARDEE: It seems to me that the term "infundibuloma" should not go unchallenged. I wonder if this tumor of the infundibulum is not really a tumor of blood vessels. If a tumor is called an infundibuloma, one thinks of it as a tumor of the nerve structure of the infundibulum. I do not pretend to be a neuropathologist. Nevertheless, Dr. Globus has said that this is a vascular tumor, and, if so, it should be named a vascular tumor located in the infundibulum rather than an infundibuloma.

DR. JOSEPH H. GLOBUS: As to the case reported by Dr. Sachs, I should not be at all surprised, had it been studied histologically, that the tumor would have been found to be a cystic hemangioma. It was most probably so, for almost all of the hemangiomas in our group are cystic. It is in accord with the view maintained by us that such tumors, in spite of the fairly large number of inert glia cells, are preponderantly vascular, belonging to the hemangiomatous type, which is most frequently associated with cyst formation and is often mistaken for cystic glioma.

As to the term "infundibuloma": All tumors contain blood vessels in a varying degree. Some are extremely rich in blood vessels, as in the case of the so-called spongioblastoma. If the tumor under discussion had the ordinary type of blood vessels, I certainly should not have been able to identify it as a special form of neoplasm. On the other hand, one need but recall the picture of a tumor type, such as a pinealoma. It is a tumor rich in blood vessels; in spite of its voluminous blood supply, however, it is not to be grouped with the hemangioma, but in view of the characteristic type of cells, the peculiar arrangement of the cells simulating the structure of the developing pineal body, is recognized as a pinealoma. Similarly, a tumor traced to remnants of the craniopharyngeal duct is termed a craniopharyngioma.

In the case of infundibuloma, Dr. Pardee had in mind the posterior lobe of the hypophysis as the source of the tumor, but I have stressed the infundibular stalk, a structure which has a distinguishing feature. It reveals during part of its developmental period an unusual vascular pattern, consisting of peculiar blood vessels. The cells, which are not quite distinctive when seen with these blood vessels, constitute a tumor which duplicates the infundibular stalk in its developmental phase. Although identified by its peculiar blood vessels, it need not, however, be classed with hemangioma, but fully deserves the name of infundibuloma.

DR. IRVING H. PARDEE: What is the structure of the infundibulum in early life, just before birth or just after?

DR. JOSEPH H. GLOBUS: There is little difference between its structure shortly before birth and that just after. This vascular character is found months before and years after birth.

Cortical Localization of Taste in Man and Monkey. DR. WALTER A. BÖRNSTEIN (by invitation).

The sense of taste is closely related to two other senses, smell and the somesthetic modality of the trigeminal nerve in the tongue. It is, furthermore, in mutual relation with sensations serving the organs of digestion, i. e., with afferent and efferent general visceral pathways, from the mouth to the intestine. Is one or more of these three functional relations expressed by close topical relations of the respective cortical areas? Some experimental and many clinical reports have been taken as evidence that the cortical taste and olfactory areas are closely adjacent or identical. However, anatomic and physiologic facts point distinctly to the postcentral portion of the central operculum, area 43, as the site of the cortical taste area in man. This assumption has been proved experimentally and confirmed by experiments on the monkey (Börnstein, W.: Beitrag zur Frage der Differentialdiagnose kortikaler und subkortikaler Herde [Kau-, Schmeck-, Hörtrias], *Klin. Wchnschr.* **7**:2343, 1928; The Cortical Taste Area in Monkeys and a Semi-Quantitative Method of Testing Taste in Monkeys, *Am. J. Physiol.* **129**:314, 1940; Cortical Representation of Taste in Man and Monkey: I. Functional and Anatomical Relations of Taste, Olfaction and Somatic Sensibility, *Yale J. Biol. & Med.* **12**:719, 1940; II. The Localization of the Cortical Taste Area in Man and a Method of Measuring Impairment of Taste in Man, *ibid.* **13**:133, 1940).

The olfactory receptors of man have preserved the primitive structure of invertebrate sense organs, but the gustatory receptors are of the same structure

as highly organized receptors of general visceral and of somatic sensibility. The olfactory fibers run to the telencephalon, but the taste fibers run to the metencephalon and the myelencephalon, and they are intimately associated with general visceral fibers from the mouth, pharynx and larynx. Their common nuclei in the first synapse are closely connected with the trigeminal system throughout the whole scale of vertebrates (Ariëns Kappers, C. U.: Der Geschmack, perifer und central, zugleich eine Skizze der phylogenetischen Veränderungen in den sensiblen VII, IX und X Wurzeln, *Psychiat. en neurol. bl.* **18**:82-138, 1914). The trigeminal system is represented in the postcentral gyrus. The efferent visceral fibers for the intestinal tract arise from area 6 (Watts, J. W., and Fulton, J. F.: Intussusception—the Relation of the Cerebral Cortex to Intestinal Motility in the Monkey, *New England J. Med.* **210**:883, 1934) and the fibers particularly for mastication, salivation and swallowing from area 6bα, which is adjacent to area 43 (Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938).

Physiologically, smell is largely a distant receptor, but taste responds largely to stimuli arising within the body. Sensory-motor correlation is unimportant for smell but is important for taste (Börnstein, W.: Ueber den Geruchsinn, *Deutsche Ztschr. f. Nervenh.* **104**:55-77; 78-91; 173-207, 1928).

A method of testing with solutions of graduated concentrations (Börnstein, W.: *Yale J. Biol. & Med.* **13**:133-156, 1940) revealed impairment of taste in 11 patients with bullet lesions in the central operculum. In 2 of these patients the precentral portion (area 6b) of the central operculum was severely and its posterior portion slightly damaged. Impairment of taste was slight. In a twelfth case the precentral portion of the central operculum was damaged; its postcentral portion was intact. Taste was unaffected. One of these patients had epileptiform attacks consisting in loss of appetite, a manifestation which seemed to point to involvement of the afferent general visceral pathways and which appeared to be a counterpart of the phenomenon of "morbid hunger," as described by Fulton (Physiology of the Nervous System, New York, Oxford University Press, 1938) and others. The cortical areas subserving taste and digestive functions are, then, in close topical relation to that cortical region which regulates "hunger" conditions.

Taste experiments on monkeys which I carried out in the physiologic laboratory at Yale University were based on the fact that monkeys prefer solutions of sugar to water and water to solutions of salt, citric acid and quinine in concentrations above those of the "preference taste threshold." These threshold concentrations were determined. The ratio of intake of water to intake of taste experiment solutions was, furthermore, determined for several supraliminal concentrations. Impairment in taste was characterized by rise of threshold values and by fall (or abolishment) of preference for the supraliminal concentrations. Several thousand trials were made.

Impairment of taste was determined on 3 monkeys after bilateral lesions of the sensorimotor face area, but not of either the sensory or the motor face area alone. (Evaluation of the results of experiments on a fourth monkey has not yet been completed.) Recovery remained incomplete during the observation periods, which varied from seven to ten months after the final operation.

The results of studies of retrograde thalamic degeneration in these brains (to be published with A. E. Walker) are in essential agreement with preliminary results of other taste experiments in this series (unpublished observations of T. C. Ruch) conducted after destruction of the arcuate nucleus with the Horsley-Clarke technic.

Prof. J. F. Fulton performed the operations.

DISCUSSION

DR. TRACY J. PUTNAM: I should like to ask Dr. Börnstein whether he feels that his experiments indicated that the slight recovery of the sense of taste which he noted was due to incomplete extirpation of the cortical area or whether

it was the result of taking over of the gnostic sense of taste by subcortical structures.

DR. WALTER A. BÖRNSTEIN: The impairment of the sense of taste differed in different animals and for different taste qualities, and so did the recovery. The degree of recovery might have been due to some extent to incomplete extirpation. However, Green and Walker (The Effects of Ablation of the Cortical Motor Face Area in Monkeys, *J. Neurophysiol.* **1**:262-280, 1938) have shown that subcortical structures play some role in recovery of the motility of the face, after corresponding ablations, and the same is likely to be true for the recovery of taste.

Some years ago Dr. Putnam mentioned the fact that pain and pleasure "are so closely mingled that . . . they may even be indistinguishable" (Pain, *Hygeia* **16**:686-688 and 746-747, 1938). Sensations of pain and pleasure are conveyed by somesthetic and general visceral pathways. It could be shown today that the sense of taste is closely akin to these two systems. Does a corresponding relation exist between two qualities in the sense of taste? Certain facts suggest, indeed, that bitterness and sweetness are also closely related to each other; the association of bitter after-sensation with many sweet tastes, for example, points in this direction. Furthermore, painful and bitter stimuli are, to my knowledge, the only two kinds which arouse avoiding reactions in vertebrates, from fish to man. Do bitter stimuli produce nervous processes which are in some respect like those produced by pain stimuli? These questions might be approached by examination of peculiarities of conduction, such as has been suggested by Lashley (The Thalamus and Emotion, *Psychol. Rev.* **45**:42-61, 1938) for examination of the affective character of "painful and pleasurable sensations," and by examination of relations to visceral reflexes, such as has been performed by Cannon (Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement, ed. 2, New York, D. Appleton and Company, 1929).

It seems to me that certain more general problems of sense physiology can be approached more easily in the field of taste than in other sensory fields and that the results obtained will contribute to understanding of the physiology of the central nervous system.

Innervation and "Tonus" of Striated Muscle in Man. DR. PAUL F. A. HOEFER.

This paper will appear in full, with discussion, in a future issue of the ARCHIVES.

PHILADELPHIA PSYCHIATRIC SOCIETY

O. SPURGEON ENGLISH, M.D., *Vice President, in the Chair*

Regular Meeting, May 16, 1941

Agitated Depressions. DR. H. CRAIG BELL and DR. THEODORE L. DEHNE.

This paper constitutes a study of 51 patients admitted to Friends Hospital, Philadelphia, between October 1938 and April 1941 whose illness was diagnosed as agitated depression. Of these 51 patients 12 were men and 39 women. The men ranged in age from 35 to 67 and the women from 33 to 70. For purposes of classification, the condition of 6 of the men was diagnosed as manic-depressive psychosis, and of 6 as involutional melancholia, while 12 of the women were considered to have a manic-depressive psychosis and 26 involutional melancholia.

The 51 patients presented fairly typical clinical pictures. The most common symptoms were restless pacing, anxious facial expression, somatic delusions, often

of a bizarre type, hypochondriacal ideas, delusions of persecution and self-accusatory ideas centered chiefly about more or less minor sexual aberrations. The prepsychotic personality of the patients in this group followed unusually definite and clearcut patterns. The outstanding characteristics were meticulosity, perfectionism, limited and fixed personal interests and an underlying chronic feeling of insecurity and inability to adapt to changing situations. Most of the patients could be classified as introverts.

Electric shock therapy used in the cases of 5 men and 6 women materially reduced the expected period of hospitalization.

It is concluded that the agitated depression may occur from early adult life to the eighth decade and may commonly recur, that the prepsychotic personality of patients so affected follows a distinct pattern, as does the symptomatology, and that the agitated depression differs markedly from true manic-depressive psychosis.

Electric Shock Therapy: Preliminary Report. Dr. James H. Closson and Dr. Charlotte E. Swaney (by invitation).

The paper presents a preliminary report on the first 20 patients treated with electric shock in Friends Hospital from October 1940 to April 1941.

The majority treated were suffering from affective psychoses; contraindications included an arbitrary age limit of 65, advanced arteriosclerosis, cardiac abnormalities with symptoms referable to these cardiovascular changes, a positive Wassermann reaction of the cerebrospinal fluid or other evidence of organic disease of the central nervous system, tuberculosis or malignant disease and spinal abnormalities, of which arthritis was the most common.

Routine pretreatment studies included physical and neurologic examinations, laboratory studies of the blood and urine, chemical analyses of the blood and roentgenographic examination of the spine.

Treatment consisted in application to the head of an alternating current of 120 to 140 volts and 120 to 240 milliamperes; resistance was always reduced below 1,000 ohms and the current given for 0.2 second. Precautions consisted in support of the back in slight hyperextension, immobilization of joints to prevent overexcursion and use of gags to prevent biting.

The reaction was either a petit mal or a grand mal convulsion, the latter closely resembling an epileptic seizure. A series of grand mal seizures was necessary for effective treatment, and if a petit mal convulsion was obtained the current was increased in a second, and if necessary in a third, attempt to produce a grand mal seizure. The patient was immediately unconscious and remained so during the convulsion and for from five to fifteen minutes thereafter.

Treatments were given three times weekly, with at least forty-eight hour intervals. More than 10 grand mal reactions were rarely induced, and the patients who showed the greatest improvement averaged only 7 each.

Complications included headache, nausea, confusion and loss of memory, which subsided at longest within two weeks after the final treatment; a definite reversal of mood to the point of silliness, in all cases of agitated depression, with disappearance on further treatment, and fracture, which occurred once (fracture of the humerus) in this group of 20 patients. Any complaint of back or joint pain was checked roentgenographically, and 50 per cent of all patients treated were examined by roentgenogram at the termination of treatment and showed no evidence of fracture.

Of the 20 patients treated, 3 were unimproved, 8 were improved, 3 had social remissions and 6 recovered. Schizophrenic patients constituted the majority of those showing slight or no improvement. Of patients with affective psychoses alone, the number showing social remission and recovery was 70 per cent.

DISCUSSION ON PAPERS BY DRS. BELL AND DEHNE AND CLOSSON AND SWANEY

Dr. William Furst, Norristown, Pa.: I have not had the privilege of treating a patient with more than 10 to 15 electric shocks, but certain schizo-

phrenic patients had remissions after 10 treatments. After a recurrence of the psychotic symptoms, a second series of 10 treatments frequently produced another remission.

With regard to the premature termination of electric shock treatment of schizophrenic patients, I agree with the opinion expressed by Dr. Gonda at the symposium on electric shock treatment conducted at the annual meeting of the American Psychiatric Association May 9, 1941, at Richmond, Va. If such patients do not respond after 10 sessions, treatment should be continued until at least 30 have been administered. This is also the opinion expressed by Italian investigators.

Dr. Theodore L. Dehne: There are some who have submitted patients to a great many more shocks than the high of 25 at the Friends Hospital. Our average is actually a good deal lower than that. There was quite a bit of discussion at the symposium on mental health in Richmond regarding the use of large numbers of shocks. It is possible that worth while results might be obtained with large numbers of electric shocks (20, 30 or 40) in cases of schizophrenia.

Dr. Samuel Cohen: Generally, the results of treating the affective disorders are far more encouraging than those of treating schizophrenia. (Dr. Cohen cited the case of a patient in a state hospital for four years who received 70 treatments and survived.) As a rule, I believe insulin is the treatment of choice for schizophrenia.

What was the duration of illness of the schizophrenic patients receiving electric shock?

I have noted that catatonic patients emerge from their stupor very readily but often slip back after electric shock. However, with additional treatment there may be favorable results.

Dr. Theodore L. Dehne: I believe the schizophrenic patients we have treated with electric shock had conditions of long standing except 2, whose cases were not included in the statistical study. Actually, we much prefer insulin to electric shock therapy for schizophrenia, but have used electric shock more or less experimentally. One patient, a young woman in a catatonic stupor, was very well after her third or fourth electric shock, but after her seventh she was observed to be in the condition in which she was admitted to the hospital.

Dr. Herbert Freed: At Philadelphia General Hospital schizophrenic patients were given 40 treatments with metrazol—a course of 20 shock treatments, with improvement and subsequent relapse, and a second course of 20 treatments, with repeated relapse.

It seems to me that there are still great differences between the reactions of patients to metrazol and those to electric shock.

Two patients who did not respond as well to electric shock as I had expected they would, were given metrazol and showed a surprising degree of improvement. Perhaps I did not give electric shock therapy a long enough trial, and the improvement with metrazol may have been due in part to the time element. However, there is still a great deal to be worked out with regard to responses to various forms of convulsive treatment.

Dr. Joseph Hughes: It might be interesting to hear from Dr. Sielke, of the Philadelphia State Hospital, who has been treating a large number of schizophrenic patients. We should like to have his point of view regarding the effectiveness of electric shock therapy for this psychosis.

Dr. Eugene L. Sielke: There is a very large group of patients with chronic schizophrenia at the Philadelphia State Hospital—patients who have remained there for several years, who have regressed and are of the backward type. This was the material for electric shock therapy.

Six patients received a total of 45 treatments, without alteration of the condition or complications. Improvement, when it was noted, usually appeared within 3 or 4 treatments, although 10 treatments might be given, with improvement after the seventh or eighth. After improvement began some of these patients

were given 1 treatment a week rather than the usual 3. This is merely a brief preliminary estimate. The group has been under observation only two months, and the time is too short for the report of definite results.

DR. WILLIAM FURST, Norristown, Pa.: My associates and I have given 5 patients who showed little progress under insulin shock treatment 3 electric shocks a week, which we alternated with 3 insulin shocks a week after the patient had had 30 insulin treatments. Three of these patients responded favorably.

DR. FREDERICK H. ALLEN: I have had no experience with the actual procedure of shock therapy. However, in the discussions I have not heard enough emphasis on the psychotherapy which should accompany or follow the shock treatments. Too frequently shock therapy is regarded as a form of treatment apart from well established principles of psychotherapy. It should be a means rather than an end in itself. The time when shock therapy is over might be a favorable one for establishing a good relation with a patient and helping him in his inner readjustments, an opportunity which might not be possible without this preliminary aid. I regard as a step backward any treatment that simply gives a patient a series of shocks and then leaves him alone. I should like to see the psychotherapeutic side of shock therapy stressed a great deal more.

DR. THEODORE L. DEHNE: When we first began to administer electric shock, as soon as the patient was demonstrably improved and was accessible, we made an attempt to carry out regular psychotherapy without further electric shock. Only recently have we set a limit of 10 treatments to a series.

DR. EARL D. BOND: I am glad that Dr. Dehne and Dr. Bell discussed the agitated depression as more than simply a symptom complex of the menopause. The term rigid describes the personality amazingly well. Since the rigid personality is so important, it becomes of interest to know how soon one can discover it. In some studies of college students one of the personality types that stands out is the "just so," very particular, unyielding variety.

I agree that many patients past the age of 65 should not be accepted for electric shock treatment. However, if the prognosis is bad, because of arteriosclerosis, why should one not take some risk to bring to the patient several months or years of normal life? The prognosis without electric shock is bad anyway.

In the case of a patient of 46 with an agitated depression, my associates and I are wondering whether by using electric shock therapy we should take the risk of adding to a memory defect which seems already to be present.

DR. JOSEPH HUGHES: The results obtained with electric shock therapy at the Friends Hospital are similar to those reported by the other psychiatric hospitals in Pennsylvania and New Jersey. At the recent meeting of the American Psychiatric Association in Richmond, Va., all of the hospitals administering electric shock therapy in this area combined in an exhibit presenting the results of the treatment. The rate of recovery from the agitated depressions was between 70 and 75 per cent. The rate of recovery for the schizophrenic group was no greater than that obtained with general psychiatric treatment.

An experimental study of the effect of electric shock on the brains of cats has revealed that petechial hemorrhages occurred in a high percentage of animals. From this it may be presumed that such hemorrhages could occur in man after repeated electric shock treatments. However, there is no positive proof of this at present. I do not believe that the possibility of such damage should deter one from this type of treatment, for clinically the therapeutic results obtained far outweigh the danger.

DR. O. SPURGEON ENGLISH: Like Dr. Allen, I wonder why there is so little interest in the psychologic manifestations of the results of this treatment. Certain attitudes of the manic-depressive personality have struck me as day after day I have carried out psychotherapy on such patients.

First the manic-depressive patient seems to me to be a person with great poverty of emotion and ideas, which traits are usually regarded as particularly characteristic of schizophrenia. One may attempt to get such a patient away from one or two ideas to which he holds, but he fights one off passively, but so effectively! His attitude seems to say: "You cannot touch me emotionally." One speaks of regression in a psychosis. One sees this in patients with manic-depressive illness, whether they are agitated or whether they are like heedless children—certainly they are affectively heedless, cold and unresponsive.

I have the impression that electric shock treatment gives the depressed person a "spanking" and at the same time allows him to discharge large quantities of aggression. Some claim that this cannot be so since the patient has no memory for the shock itself. To my mind that makes no difference. I believe these affects are registered subconsciously, if not consciously. There is not much difference between electric shock therapy and metrazol therapy—the effect of the convulsive activity being the same.

One notes in the catatonic patient a great fantasy life—taken up with hallucinations and delusions—a means which a depressed patient cannot utilize, since he clings so steadfastly to rigidity in thought and feeling.

I understand that the response to the Rorschach test of the manic-depressive patient is nearest normal; this must correlate with the commonly accepted belief that manic-depressive psychosis is much more benign than schizophrenia. However, like Dr. Allen, I believe that electric shock should be looked on not as an end in itself in treatment of affective psychoses but merely as a research tool for finding out more about the nature of affective states. The latter cannot be accomplished without more data concerning the patient's thoughts and feelings in relation to electric shock.

DR. THEODORE L. DEHNE: One sees the intense lack of imagination and self-centered interest in patients of this type. They are as unresponsive to any type of abstract thinking as any group of patients we have seen.

DR. ALEXANDER SILVERSTEIN: Have the authors performed any neurologic examinations on patients after electric shock therapy?

In several instances neurologic examinations of patients who had received electric shock therapy (from fifteen minutes to several hours after treatment) revealed such pathologic signs as increased reflexes, the Babinski sign and the ankle clonus. In 1 instance the Babinski sign persisted for more than twenty-four hours.

DR. WILLIAM FURST, Norristown, Pa.: It is the consensus that the neurologic changes following electric shock are insignificant and only transitory. Grinker, however, stated that minor neurologic changes could be noted in almost all patients after electric shock if a careful examination was made. Transitory appearance of the Babinski sign is common.